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THERAPEUTIC EFFECTS OF LSD: A FOLLOW-UP STUDY

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Lysergic acid diethylamide (LSD) has been used to treat many psychiatric patients, but its status as a therapeutic agent remains uncertain and controversial. Specific indications for therapy with LSD have not been established, although there is some evidence that patients with conduct disturbances, *e.g.*, chronic alcoholics and sexual deviates, tend to respond favorably even to limited treatment (3, 4). The present investigation was carried out in an attempt to define some indications for LSD therapy and to develop prognostic indicators. The study was divided into two phases: the first focused on the relationship between insightful experience produced by LSD and swift clinical improvement; the second extended the study to evaluate the stability of this improvement by studying the patients a year after LSD treatment.

Results of the first phase have been reported previously by Eggert and Shagass (6). This aspect of the study was designed to test the assumption that patients who react to LSD with an insightful response are more likely to show favorable behavioral change than those who do not. One aim was to determine clinical criteria predictive of insightful response. Other authors have used terms such as "mystical," "cosmic," "psychedelic" and "consciousness-expanding" to designate the insightful response (7, 8). For the purposes of this study an insightful response occurred if, during an LSD session, the patient experienced early memories and altered his perception of his relationships to the world; if he related these memories and fresh perceptions to his present problem; and if he made a convincing resolution to change his future behavior as a consequence of his new understanding.

Patients who responded to LSD therapy with insightful experiences of this kind were distinguished from those who showed no such response by raters who listened to tape recordings of the sessions. Eight patients were classified as "responders," and 12 were classified as "nonresponders."

Seven of the eight responders were found to be among nine patients who had been diagnosed as psychopathic personality because they showed five of 15 criteria for this diagnosis designated in the Small (10) structured interview. The results, demonstrated a significant relationship between psychopathic personality characteristics and a tendency to react to LSD with an insightful response. It was also found that no subject under 22 years of age was classified as a responder.

The present report deals with results from the second phase of the study, a follow-up evaluation of the same 20 patients after one year. Obviously, the prognostic value of predicting immediate insightful response to LSD depends upon the later clinical course associated with the type of immediate response. Although the answer to this question rests on comparisons of outcome in the responder and nonresponder groups, the design of the follow-up study also permitted comparison of outcome in all patients treated with LSD with that of a matched group of patients who were not given LSD.

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This study was conducted at the Psychopathic Hospital, Iowa City, Iowa. The cooperation of the medical staff, directed by Dr. Paul E. Huston, is gratefully acknowledged. Sandoz Pharmaceuticals supplied the LSD.

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METHODS

SUBJECTS

Subjects were 20 psychiatric inpatients at the Psychopathic Hospital, Iowa City, Iowa. All submitted voluntarily to treatment and signed a special experimental treatment release form. A deliberate attempt was made to recruit patients with conduct disturbances. Ten subjects were court-referred or had some legal problem related to psychiatric contact. Ages ranged from 16 to 36 years (median, 24); 13 were men. Selection precedures were designed to exclude subjects with overt psychoses, mental retardation and brain syndromes. Small's (10) structured interview was used to clinically evaluate patients prior to LSD administration. All responses to standard questions were recorded verbatim on a protocol sheet; these were then used to complete a check list of diagnostic criteria, which led to classification according to predetermined rules. Although the classification system differs in some respects from that of the American Psychiatric Association, use of the Small procedure insures greater reliability because it reduces variability. By this method the patients were grouped in the following diagnostic categories: psychopathic personality, nine cases; exogenous depression, five; psychoneurotic reaction, four; schizophrenic reaction, one; no diagnosis, one. The patient diagnosed as schizophrenic reaction was not at the time obviously psychotic, although later observation verified this diagnosis. No patients received drugs for at least 48 hours before test injections; only five had taken medications for their present condition.

TREATMENT PROCEDURE

LSD was administered intravenously at a dose of 2.5 mg/kg body weight. In this group it was given only once. The intravenous method was used to speed the action of the drug and to reduce variability of response due to absorption differences. Preparation for the drug sessions consisted of at least six interview hours over a seven- to 14-day period. In these interviews current problems were explored and subjects were informed that the drug session could lead to unusual and important experiences. Sessions took place in the office of the investigator who administered the drug and stayed with the patient almost continuously from 9 a.m. until evening; he attempted to maintain a supportive, interested and generally nondirective attitude. At bedtime chloropromazine, 25 to 50 mg, was administered. Twelve patients also received 20 mg of methamphetamine intravenously on another day (alternate order of administration) in an attempt to compare the effects of the two drugs. However, it was found that observers could easily distinguish between LSD and methamphetamine.

CLASSIFICATION OF INSIGHTFUL RESPONSE

Degree of insightful response to LSD was rated independently by two psychiatrists, not otherwise involved in the study, from tape-recorded samples of the LSD session totaling about 60 to 90 minutes. Ratings were on a scale from 0 to 3+. The raters had available full routine case material about each patient but not the structured interview data. A 3+ rating was assigned to sessions in which there was reliving of forgotten childhood experiences, integration of this material, and realistic self-acceptance with the resolution to improve. Ratings of the two observers were identical in 11 of 20 cases and within one point in 18 of 20. Ratings were skewed toward the zero end of the scale, but it was possible to divide the cases into those responding more and those responding less by taking a mean rating of 1.0 or more to indicate a responder.

FOLLOW-UP PROCEDURE

Case histories were reviewed, and a list of symptoms and deviant behavior char-

acteristic of each LSD patient was compiled. For every patient treated with LSD the hospital records were searched to find a patient treated by means other than LSD, who would match the LSD case closely for age, sex, marital status, years of education, psychiatric diagnosis, and for his pattern of symptoms and deviant behavior. Due to the large number of hospital cases available, it was possible to achieve satisfactory matching. Two examples presented in Table 1 illustrate the similarity of clinical features in LSD and control patients. All LSD cases and their matched controls were contacted by letter; letters were also sent to significant relatives such as parents and spouse. If the letter did not elicit a response, telephone calls were placed. Appointments were then made for both the patients and their relatives to be seen and interviewed. Those who could not come to the hospital were interviewed by telephone, as were the relatives. In one instance, the whereabouts of the patient was unknown, so only his wife was interviewed. In another case, the patient was in prison, and an interview was conducted by the prison psychiatrist, who followed a prescribed interview schedule.

Each patient and relative was asked to rate changes in symptoms and deviant behavior listed for that patient at six months and 12 months following treatment with LSD, or following discharge from hospital in the group not treated with LSD. The patient and his relative were also asked to note improvement in any particular aspect of behavior. If there had been improvement, they were asked to rate its degree on a 4-point scale with steps defined as 25, 50, 75 or 100 per cent. A 100 per cent improvement was indicated if the behavior or symptom in question was no longer a problem to the individual or his family. Improvement ratings were coded on a scale from 0 to 4, and the ratings of the patient and his relative were averaged for each manifestation.

TABLE 1

Two Examples of Case Matching

Manifestation Rated	LSD Case	Control
Case 1		
Dexedrine habituation	*	*
Overt homosexuality	*	*
Excessive use—other meds.	*	*
Poor relationship to females	*	*
Anxiety and depression	*	*
Feels sexually inadequate	*	*
Case 2		
Checks with insufficient funds	*	*
Embezzlement ($13,000)	*	
Extorting money from people		*
Lying	*	*
Excessive drinking	*	*
Sexual promiscuity	*	*
Conflict with authority	*	*
Poor work record	*	*
Gambling	*	
Irresponsible to family	*	*
Feels inadequate	*	*

* Indicates presence.

RESULTS

In view of the diversity of symptom and behavioral manifestations, it seemed reasonable to compare overall ratings of clinical change. The change ratings from 0 to 4 were averaged to achieve a single overall change rating at six and 12 months for each patient. Mean ratings were then compared for the LSD-treated and non-LSD-treated group and for the LSD responders and nonresponders. A summary of the follow-up results is shown in Table 2. Statistical significance was evaluated by means of t-test (two-tailed). It is seen that the LSD-treated group at six months was rated significantly more improved than the control group ($p < .05$). At 12 months, the LSD group still showed greater improvement ($p < .02$). Within the LSD group, those who had insightful responses during the LSD session were considered much more improved at six months than those classified as nonresponders ($p < .001$). The LSD responders were still significantly more improved than the nonre-

TABLE 2
Follow-up Results

Subject Group	Mean Ratings of Overall Change	
	At 6 mos	At 12 mos
LSD (N = 20)	1.69 ± 0.39*	1.94 ± 0.30
No LSD (N = 20)	0.82 ± 0.20	1.03 ± 0.20
p	<.05	<.02
LSD responders (N = 8)	3.09 ± 0.45	2.51 ± 0.46
LSD nonresponders (N = 12)	0.76 ± 0.32	1.55 ± 0.38
p	<.001	<.02
	Change from 6 to 12 mos	
	Mean	p
LSD responders (N = 8)	−0.58 ± 0.27	.10
LSD nonresponders (N = 12)	0.79 ± 0.19	<.01
No LSD (N = 20)	0.21 ± 0.12	.10

* Standard error of mean.

TABLE 3
Comparisons with Respect to Some Behavior Areas

Behavior Area	Mean Rating of Change	
	6 mos	12 mos
A. Sexual*		
LSD responders (N = 6)	3.83	2.83
LSD nonresponders (N = 5)	2.00	2.00
No LSD (N = 11)	1.64	1.64
B. Excessive alcohol or drugs		
LSD responders (N = 5)	2.80	2.40
LSD nonresponders (N = 4)	0.25	0.50
No LSD (N = 7)	0.00	0.00
C. School, home or job performance		
LSD responders (N = 5)	3.20	1.60
LSD nonresponders (N = 8)	0.00	0.88
No LSD (N = 13)	1.08	1.62

* Homosexuality, frigidity, impotency, promiscuity.

sponders at 12 months ($p < .02$), but the difference was not as great.

Table 2 also shows the mean change in ratings of improvement between six and 12 months and the significance of the difference. Only the LSD nonresponders showed acceptably significant continuing improvement ($p < .01$). Clinical improvement tended to recede between six and 12 months in the LSD responder group.

The data were examined to determine whether particular behavior or symptom areas showed greater change in response to LSD; responders and nonresponders were also compared along these lines. Table 3 shows some comparisons in three behavior areas. The small number of cases precluded meaningful statistical tests on these findings. However, the LSD responders showed more improvement than any other group in the areas of sexual behavior and excessive use of alcohol or drugs. On the other hand, in ratings of school, home or job performance, the considerable improvement of the LSD responder group at six months had largely vanished by the 12-month period, so that these patients had the same mean change rating as the group which did not receive LSD.

DISCUSSION

The results indicate that, as a group, patients treated with LSD showed more improvement than similar patients not so treated. Furthermore, the LSD patients who showed the greatest clinical improvement were those who displayed an insightful response during or within 24 hours of the single LSD treatment session. These pa-

tients, most of whom had disorders of conduct, were initially diagnosed as psychopathic personalities with the Small structured interview (10). The findings suggest that Small's criteria for this diagnosis can be used to select candidates for LSD therapy. An immediate check on the adequacy of selection is provided by the LSD treatment session itself; for those patients who experience an insightful response can be expected to show relatively swift clinical improvement. Since only those patients who were 22 years of age or older showed insightful responses to LSD, age may also be an important variable.

Although results from the follow-up study clearly indicated that the LSD group showed more improvement than the matched control group, it seemed possible that the difference might be due to other forms of psychiatric treatment. That is, patients in the LSD group might also have had more follow-up treatment than control patients. When case records were examined to check this possibility, the results confirmed the opposite conclusion: three LSD cases had weekly psychotherapy in the year following treatment, but 13 control cases had weekly psychotherapy during this period.

It is of interest that the patients given LSD and classified as nonresponders tended to show significant improvement in a more gradual manner, so that they were rated as more improved at 12 months than at six months. In contrast, the LSD responders improved dramatically almost immediately but tended to show signs of relapse at a mean interval of about seven months following their LSD session.

Certain aspects of the study are clearly open to criticism, particularly the fact that the interviewer knew which patients had received LSD. It would be extremely difficult to avoid this problem, because of the distinctive effects of LSD. It can only be stated that the interviewer attempted to avoid interpretation of the ratings of change given by the patient and his relatives. Different clinical outcomes also could have resulted from differential motivation for treatment. However, this seems unlikely since ten patients of the LSD group were court-referred or had some legal problem relevant to hospital admission, such as threat of divorce; and similar legal problems were present in nine of the patients not treated with LSD. It is also obvious that the group was small and that any generalizations based on a small sample must be viewed with great caution. However, similar findings have been obtained by other workers from different countries. For example, Johnsen (7) noted in his large series of cases that sexual perverts and psychopaths frequently had "deep emotional reactions with cosmic and mystic experiences" to LSD, whereas compulsive neurotics rarely reported such experiences.

Some LSD patients interviewed in the follow-up study indicated that they had recently begun to relapse and asked for additional treatment. One such case was a 25-year-old homosexual man who had achieved his first heterosexual intercourse six weeks after his LSD treatment and had managed to establish a relatively stable relationship with a woman until about eight months following this treatment. At this point he had begun to have homosexual fantasies once again and had stopped dating. He was readmitted for another LSD treatment session, after which he felt that he had solved his problem. But he returned again after one month saying that he feared a relapse. He was readmitted once again for an additional treatment. At this time he stated that he was certain that his problem was solved. Following this third LSD session he left the hospital confident that he could maintain a heterosexual adjustment and he has succeeded in doing so for many months. Such cases suggest that follow-up contact after LSD

treatment is desirable and that readmission for further sessions should be very seriously considered when there is impending relapse. It is noteworthy that most cases of relapse did not occur suddenly; as in the case cited, an interview would be likely to disclose the change in fantasy content which could be used as indication for further therapy.

It is also possible that a series of concentrated LSD sessions may yield results superior to those obtained with single treatments. In an LSD study currently in progress we have found several patients in whom insightful response appeared only with a second or third injection of LSD. In no case did a fourth treatment produce an insightful response when the first three had failed to elicit one.

Workers using LSD for psychotherapeutic purposes have frequently introduced adjunctive procedures, such as intensive psychotherapy and hypnosis (2) or sensory stimulation, such as music and pictures into the LSD sessions. We used no procedures of this kind. We deliberately refrained from interpretive comments, assumed a nondirective attitude, and allowed the patient to arrive at his own insights during the LSD sessions and subsequently. Despite this nondirective approach, the responses of the patients, *e.g.*, insights concerning their relationship to the world and realization of the need to respect other persons' dignity, were similar to those recorded by other observers using more forceful psychotherapeutic intervention (4). Many of our patients were motivated by external pressures to seek treatment for problem behavior, and, in our psychotherapeutic preparations for the LSD session attempts were made to define the behavior problem which required assistance. The working hypothesis underlying this approach is that *the probability of favorable behavioral change with LSD is increased in individuals in whom the behavior to be changed can be specified.* It follows that problems, such as homosexuality or consuming too much alcohol, might be more amenable to change than those which involve multiple activities and which can be described only in a general way, *e.g.*, passive-aggressive behavior. Our results support this expectation.

General personality assets of patients may also furnish prognostic cues for LSD treatment. Patients with good ego assets in spheres other than their personality deviation appeared to show more favorable change. The apparent relationship between favorable result and age may also be a function of the level of personality development.

It is important to emphasize that LSD treatments were administered to hospitalized patients under closely supervised conditions and that careful observation was maintained for at least 24 hours after the treatment. These conditions were instituted at the beginning of our work with LSD in accordance with a general attitude of caution and maximal safety. The necessity of such careful supervision is documented by recent reports of prolonged adverse reactions to LSD (5). Although careful selection of patients will, hopefully, minimize possible complications of LSD therapy, they can be recognized and dealt with only in a controlled setting. Furthermore, it seems possible that the supervised setting, designed to diminish the patient's anxiety as well as to promote safety, may be an essential condition for therapeutic benefit.

Several observations raise questions about the duration of LSD effects and their relation to the immediate response. The fact that the LSD-treated nonresponder group showed continuous improvement between six- and 12-month follow-ups raises the question, "Can one LSD experience facilitate personality growth over

a long subsequent period of time, even though there is little immediate behavioral change?" The tendency of those who showed the greatest immediate behavioral change to relapse after several months gives the impression that, in some way, effects of the drug could have continued to be present for several months before they gradually disappeared. Observable neurophysiological changes produced by one dose of LSD in man are usually no longer evident after 24 hours (9). However, Adey *et al.* (1) observed some electrical effects lasting for about a week after LSD in the hippocampal regions of the cat, so that long-lasting functional changes in some brain areas seem quite possible.

Results to date support the view that immediate and subsequent reaction to LSD may be predicted from clinical observations and that the drug has favorable therapeutic benefits in a category of patients otherwise very difficult to treat. Further exploration of the use of LSD in treatment appears indicated; and research elucidating the mechanism of action of the drug should contribute in an important way to psychiatric pathophysiology.

SUMMARY

Twenty psychiatric patients treated with a single large dose of LSD were studied to determine degree of improvement in symptoms and problem behavior six months and one year after treatment. Clinical change in the LSD-treated group was compared with that in a patient group matched for age, sex, education, marital status, psychiatric diagnosis and clinical manifestations. The LSD group was divided into two groups: those displaying an immediate insightful response to LSD (responders) and those failing to do so (nonresponders). The responder group was found to consist mainly of patients with diagnoses of psychopathic personality and all were at least 22 years old.

Patients treated with LSD showed greater improvement than those in whom LSD was not used, even though two-thirds of the non-LSD group received systematic psychotherapy compared to only one-sixth of the LSD group. The LSD responders showed significantly more improvement than the LSD nonresponders. However, the responder group showed a tendency to relapse after six months, whereas the nonresponder group showed progressive improvement between six and 12 months.

It was concluded that patients with specific conduct disorders, who otherwise have reasonably well developed personality assets, are probably the most favorable candidates for LSD therapy. Although the probability of relapse is high after six months, successful retreatment has been demonstrated. Several possible shortcomings of the study, including the small number of cases, invite caution in interpretation of results, but they clearly encourage further study of the use of LSD in treatment.

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