Original Articles

Prolonged Adverse Reactions to LSD in Psychotic Subjects

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THE INCREASED abuse of lysergic acid diethylamide (LSD) has aroused popular concern for its complications and has led the leading pharmaceutical manufacturer to withdraw its supplies from investigational use. Recent reports, especially those in the lay press, give the impression of an increasing incidence of persistent psychoses, associating the observations with the illicit use of LSD.[1,2]

The experimental LSD experience in medical settings is usually described as transient, limited to a few hours or at most a day. The persistence of ideational or emotional changes beyond 24 hours may be defined as "prolonged effects" and these have been reported in surprisingly few subjects.[3,4] The descriptions of these prolonged adverse effects generally include spontaneous recurrences of the acute LSD experience, persistent psychotic decompensations, induced depression with attempted and completed suicides, and multihabituation. The durations of these states range between one week and two years, with about 40% of the cases not improving at the time of the reports.[1-9] While the prolonged effects generally described are those of an adverse nature, recent descriptions of the therapeutic effects of LSD in the treatment of neurotics,[5,6,10-12] psychopaths,[5,10,11] and alcoholics [8] may be viewed as "prolonged beneficial effects."

A recent study highlights the apparent increase in the incidence of the adverse reactions in one hospital.[2] In a four-month period 27 patients were admitted for the indiscriminate use of LSD. Twelve cases reported in detail exhibited panic reactions (six patients), reappearance of the LSD symptoms (two patients), overt psychosis (three patients), and the reappearance of overt psychosis with panic reaction (one patient). Seven patients were classified as suffering from schizophrenia at the time of admission, but each had varying degrees of personality difficulty before taking LSD. Eleven had previously experimented with barbiturates, amphetamine phosphate, alcohol, or marihuana.

The prolonged effects have been ascribed to the isolation of the experimental situation [3,5] and to dosage [3,5,9,13] but most often to preexisting disorders of personality and psychopathology.[2-4,8] The use of other drugs in association with LSD is an additional complication as many of the reported prolonged reactions occurred in subjects admitting to the use of other hallucinogens, stimulants, and narcotics.[1,2,4,9]

The incidence of prolonged adverse effects in each study has been too low to provide

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adequate material for a satisfactory evaluation. It is our purpose to review the prolonged changes observed in studies of LSD in a group of severe mentally ill subjects.

Methods

During a 24-month period, LSD has been administered to 65 psychotic subjects in a study of the therapeutic, neurophysiological, and linguistic effects of acute and repeated administrations. There were 158 administrations with 31 patients receiving one, 21 patients with two, and 13 patients with 3 to 15 administrations of LSD. The patients were receiving placebo medication in 120 instances and active psychotropic drug treatments in 38 instances. Dosages of LSD ranged from 0.5μg/kg to 10.0μg/kg with the majority between 1μg and 3μg/kg (60μg to 250μg). Four administrations were more than 500μg each with 840μg as the highest single dose. Administrations were usually intravenous and on occasions oral, and each was undertaken in the EEG laboratory.

The patients were psychotics with their present hospitalization of 0.3 to 28 years (average 5.1 years) with a duration of illness of 0.9 to 30 years (average 14.6 years). They had not shown significant behavioral improvement despite a variety of organic, social, and psychological treatments. Ages ranged from 20 to 53 years, with a mean age of 36.

The usual behavioral effects of LSD were an initial excitement phase of less than five minutes associated with irritability, restlessness, dilated pupils, and increased heart rate. A quiescent period of 30 to 40 minutes was followed by the gradual appearance of the more "typical" aspects of the LSD reaction. Pupils dilated, motor reflexes increased, and the subjects reported visual illusory sensations on inquiry. Disturbances in thought and elevated mood and excitement were observed. At one hour and again at two hours, the subjects were examined in a semistructured interview which was recorded for studies of the changes in language patterns. The behavioral changes achieved a maximum effect two to four hours after administration, usually waning without additional medication during the ensuing eight hours. While this was the "usual" pattern, some subjects became sedated and relaxed and failed to report the typical visual and ideational changes.

Observations

Prolonged reactions to LSD were observed in three instances in 158 administrations—an incidence of 2%. The reactions were characterized by prolonged disturbances in mood, affect, and thought accompanied by confusion with the induced changes failing to respond to active psychotropic drug treatment for periods up to three months.

Reviewing the behavioral characteristics of these subjects before the LSD reaction indicates that such descriptors as alternating emotional states, emotional and affective lability, and psychopathic features are prominent while thought disorder and disturbance of person were infrequent. At times, these patients were classified as suffering from an affective psychosis. With LSD, the manifestations were principally an exacerbation and a prolongation of these features with disorientation and a confusional syndrome appearing transiently. The persistent fluctuating emotional state, illusory sensations, and paranoid ideations reflected the interaction of the LSD state and the subject's pretreatment character structure. In part, this persistent caricature of the LSD-induced state could be predicted from the LSD symptoms. The subjects with prolonged reactions exhibited more acute confusional features and alterations in consciousness suggestive of an exogenous psychosis in contrast to those with transient reactions.

Individual Cases

CASE 1.—The illness of a 20-year-old man was characterized by bizarre behavior, temper tantrums, withdrawal, destructiveness, manic excitement, auditory hallucinations, and paranoid ideas following his father's death one year earlier. These symptoms improved transiently with psychotropic medication but for a five-month period prior to LSD administration he exhibited a volitional disorder of a psychopathic nature without acute psychotic symptoms.

During a placebo treatment period, he received three LSD administrations (40μg, 60μg, and 73μg) at weekly intervals. With the first two administrations, he became euphoric and more irritable and reported few visual illusions. The changes were small and transient.

Within two hours of the third administration he became depressed, restless, hostile, disoriented for time, and expressed delusions of guilt with auditory and visual hallucinations. That night, he slept poorly, remaining disoriented. The next few days he confabulated and was suspicious, withdrawn, and hostile. Gradually he became elated, irritable and overactive, and accosted patients and staff with petty and childish demands.

Chlorpromazine was first administered on the ninth day in daily dosages to 900 mg. As there was no apparent clinical effect during two weeks of

treatment, trifluperidol (to 4.8 mg) daily was instituted on the 50th day and maintained for 1½ months. The manic and aggressive behavior gradually disappeared and he was assessed to be at his pre-LSD state 3½ months after the LSD administration.

CASE 2.—A 25-year-old man was admitted with apathy, indifference, autism, poor communication, and blunt affect of four years' duration. He had a cyclic course of repeated hospitalizations of short duration, each time responding to psychotropic drug treatments.

During an initial placebo treatment period during this hospitalization he received a single administration of 40μg of LSD. He became restless, agitated and anxious, expressing paranoid and depersonalized thoughts. After 1½ hours the session was terminated with intravenous chlorpromazine. The next day he was withdrawn and quiet. On the third day he requested permission to accompany his mother on a visit home. While en route, he threw himself out of the moving car, sustaining minor injuries. He gave no explanation of his act (his first suicidal attempt) and became increasingly depressed, withdrawn, and expressed the wish to die. Within a week, the depression was replaced by euphoria, inappropriate affect, and uncontrollable giggling. He wandered aimlessly about the ward, slept and ate little, and was withdrawn and depressed.

As his pre-LSD state did not spontaneously recur by the 26th day after LSD administration, trifluperidol (3 mg daily) treatment was begun. During the next two months depression, insomnia, anorexia, and ideational disturbances gradually abated. He was less withdrawn and expressed the desire for his release and a job. The ideational disturbances never fully abated, however, and after four months fluphenazine was substituted for trifluperidol. The ideational symptoms resolved and he has been recommended for discharge, eight months after admission to the unit.

CASE 3.—The third patient was 48 years old with a 17-year history of phasic illnesses of stuporous states and withdrawal, disturbed and aggressive behavior, auditory and visual hallucinations, inappropriate laughter and fears, and thoughts of persecution. His illness began at 21 years of age at a time when a brother and a sister also suffered from psychotic illnesses. During an extended hospitalization of 11 years, he had received various treatments without success.

While in a special treatment program nine months prior to the present incident, he had received a single administration of LSD (70μg) which had not altered the existing symptomatology. In the ensuing two months, he received trifluperidol (30 mg) daily. He became better oriented, expressed no hallucinations and was less aggressive, although the alternating periods of depression and euphoria continued.

Four weeks after the cessation of trifluperidol treatment, during a placebo period, he received LSD (60μg). Within an hour, he became hyperactive, restless, hostile, aggressive, elated, and expressed auditory hallucinations. His speech was irrelevant with flights of ideas; his attention, orientation, and comprehension were impaired, and he misidentified members of the staff.

Two hours later he was given intramuscular chlorpromazine (200 mg). The symptoms abated and he returned to his ward. During the next week he exhibited alternating episodes of manic and depressive behavior with rapid mood swings and confusion. He was occasionally delirious, with paranoid ideas, depersonalization and disorientation for time and place. By the ninth day, chlorpromazine (to 1,200 mg daily) was again given for 16 days, but without an apparent effect on his psychotic state. Both the manic and confusional-delirious symptoms persisted, fluctuating in intensity and duration. There was also a loss of sleep and appetite.

He was again treated with trifluperidol (to 10 mg daily), for 2½ months. His psychosis lessened, and beginning with the fourth month, he gradually improved. The psychotic symptoms disappeared with depersonalization; derealization and the delusional fears were the last to go. Five months after the LSD he was sufficiently improved to be recommended for discharge.

Comment

Prolonged adverse reactions were observed in 2% of the repeated administrations of LSD in chronic psychotic subjects. The reactions were characterized by a disorganization of affective and ideational components of the personality, and appeared as a caricature of the pretreatment psychopathological state with the novel features of a confusional-delirious state. The instances described here are similar to those described by others as "treatment-precipitated psychosis," [5] "prolonged psychosis," [1,6] "prolonged psychotic reactions," [3] "prolonged psychotic decompensation," [4] "schizophrenic or schizophreniform reactions," [9] and "extended psychosis." [2]

The subjects exhibited phasic illnesses with emotional and affective lability before LSD, and these features became exaggerated and persistent. Observers reporting instances of prolonged psychoses associated with LSD abuse in adolescent and psychopathic individuals characterize the induced state as depressive episodes, suicidal preoccupations, delusional states, and aggressive outbursts.

Thus, the hazard of LSD administration appears not to be in the precipitation of a schizophrenic-like state but rather in decreasing emotional and affective controls and inducing a persistent state of altered consciousness. From these observations, the risks appear greater in those subjects with emotional lability and psychopathic features rather than in those with more classical forms of schizophrenia. Indeed, the more typical schizophrenic subjects tolerated LSD administrations well, exhibiting behavioral, linguistic, and EEG changes for only short periods even after dosages up to 5μg/kg.

Chlorpromazine has been suggested as an effective antagonist to the acute LSD phenomena. Two of our patients received chlorpromazine nine days after the onset of the LSD psychosis, and the third received trifluperidol on the 26th day. Failure of chlorpromazine administration to alter the psychosis suggests that the acute, pharmacological related changes may already have passed and the observed effects were more personality related.

This is confirmed, in part, by the remission of the acute LSD-induced changes in the electroencephalogram. The usual EEG effects of increased average frequency, decreased α-index, and recurrent periods of desynchronization were observed during the first six hours after LSD administration but were no longer apparent 48 hours after LSD in any of the subjects. Since observing these reactions we have terminated each LSD administration by chlorpromazine (0.2 mg/kg), and since instituting such prophylactic treatment, have observed no additional prolonged reactions.

In these studies, most of the psychotic subjects expressed displeasure with the LSD experience, and few were receptive to subsequent administrations. Despite the absence of well-documented reports of habituation, special concerns have been aroused that popular abuse may lead to addiction with the same sociological complications ascribed to the use of habituating drugs. The neurophysiological effects of LSD are not characteristic of addicting drugs. Repeated daily administrations in dosages used experimentally result in the rapid development of tolerance, and despite increasing dosages, the behavioral, neurophysiological, and autonomic effects rapidly disappear. Cross-tolerance has also been described with mescaline[14,15] and psilocybin.[15,16] To obtain the LSD effects on repeated administration requires intervals of at least three to seven days.[14,17-19] From these observations, the probability of habituation, with attendant withdrawal phenomena seems unlikely, although the use of higher dosages may elicit different behavioral responses.[20]

The prolonged reactions described here, and those described by others, are adverse in type. In a similar context, the recent therapeutic claims for LSD in various neurotic and psychopathic populations may also be viewed as prolonged effects of LSD administration. If the observations are indeed parallel, then the claims for clinical efficacy, focused as they are in psychopathic and emotionally labile subjects, will require carefully controlled studies for confirmation.

Summary

Administration of lysergic acid diethylamide (LSD) in long-term psychotic patients was associated with a 2% incidence of prolonged adverse reactions, which caricatured the predrug state with exaggeration of emotional and affective lability. The prolonged reactions were associated with an initial state of confusion and disorientation. The subjects exhibiting prolonged reactions were those who had phasic illnesses with psychopathic and emotional features as prominent aspects of their psychoses, and not those with disorders of thought or person.

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Generic and Trade Names of Drugs

Amphetamine phosphate—*Dietamine, Racephen, Amphate, Monophos, Profetamine Phosphate, Raphetamine Phosphate.*
Chlorpromazine—*Thorazine.*
Trifluperidol—*Triperidol.*
Fluphenazine—*Permitil, Prolixin.*

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