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Chapter 5

QUANTITATIVE EEG AND BEHAVIOR CHANGES AFTER LSD AND DITRAN

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NUMEROUS INVESTIGATORS have shown that indole hallucinogens differ from anticholinergic hallucinogens not only chemically and pharmacologically but also physiologically and clinically (Lebovits *et al.*, 1960; Ostfeld, 1961; Cerletti *et al.*, 1963; Rajotte, 1964; Wilson and Shagass, 1964; Itil, 1966). Drugs of the first group, the indole hallucinogens, have an aromatic or indole nucleus, whereas the potent anticholinergic hallucinogens are characterized by a phenylglycolate ring. In low dosage, indole hallucinogens induce an almost exclusive autonomic effect, predominantly sympathomimetic in character. Tachycardia, hyperthermia, hyperglycemia, and mydriasis are the most common symptoms produced in animals as well as in man. Anticholinergic hallucinogens, the second group, elicit a typical effect of mydriasis, dry mouth, tachycardia, etc. While some of these effects resemble those of the indole compounds, their underlying mechanism seems to be that of cholinergic blockade and thus differs from that of, e.g., lysergic acid diethyl amide (LSD-25; LSD).

The indole psychotomimetics can also be distinguished from anticholinergic psychotomimetic hallucinogens by their behavioral effects. The indole derivatives induce a behavior pattern that shows some similarity to "schizophrenic-like" psychosis without significant changes in consciousness (Rinkel *et al.*, 1952). Anticholinergic hallucinogens, on the other hand, produce a confusional-delirious state with varying degrees of consciousness changes that bears a resemblance to Bonhoeffer's (1910) exogenous reaction type or toxic psychosis. EEG and evoked potential investigations have also indicated that indole and anticholinergic hallucinogens differ in their mode of action (Elkes *et al.*, 1954; 1964; Wilson and Shagass, 1964). There are, however, no controlled quantitative EEG studies in which the two classes of compounds were compared; this prompted us to perform systematic comparative EEG investigations with the main representatives of the two groups of hallucinogens, LSD-25* (LSD) and Ditran** in a group of chronic schizophrenics. Our main objective was to evaluate the therapeutic value

*LSD-25, Sandoz Pharmaceuticals, Hanover, New Jersey.

**Ditran (Lakeside Laboratories, Milwaukee, Wisconsin) is a combination of two isomers, N-ethyl-pyrrolidyl-methyl-phenylcyclopentyl glyconate, and N-ethyl-3-piperidylpheny-cyclopentyl glycolate.

of both hallucinogens and at the same time to determine whether or not the effects of LSD and Ditran could be differentiated using quantitative EEG analysis and statistical procedures.

MATERIAL AND METHOD

In this study, ninety investigations in forty-five subjects were carried out. Each subject was given Ditran and LSD in comparable clinical doses; however, the records of only eighteen of these subjects (11 male and 7 female) were technically satisfactory for statistical EEG analysis. The age range of these subjects was twenty to forty-six years (average 34 years). The group was comprised of patients with schizophrenic reactions diagnosed as paranoid, four; catatonic, two; hebephrenic, four; and undifferentiated, eight. After a minimum drug-free period of eight weeks, the hallucinogens were administered intravenously at ten to fourteen day intervals as follows: LSD in doses ranging from 0.001 to 0.002 mg/kg (average of 0.0015 mg/kg) and Ditran in doses ranging from 0.004 to 0.25 mg/kg (average of 0.05 mg/kg). Additional investigations were carried out in some patients for further differentiation of both compounds and to study the interaction of LSD and Ditran with chlorpromazine. Chlorpromazine (0.05–0.5 mg/kg) was given intravenously thirty to sixty minutes after the hallucinogenic drugs.

All investigations were carried out in the EEG laboratory. EMG, EKG, and eye movements were recorded concurrently with the EEG. Blood pressure was checked every fifteen minutes. The EEG records obtained by means of the right occipital to ear or of the right occipital to frontal leads were subjected to frequency analysis on an analog system, which measured mean pen deflection (in millimeters) for each of twenty-four frequencies from 3 to 33 cps for each ten-second epoch. The Ulett-Loeffel modification of the Grey Walter frequency analyzer was used for this operation. Six to twenty-four artifact-free samples of the occipital EEG recording, each of ten seconds' duration, were selected by the technicians for analysis and statistical procedures before the injection of hallucinogenic drugs and twenty-five minutes after injection. The EEG records from the same leads used in the analog frequency analyzer were also recorded on tape and later subjected to period analysis (Burch *et al.*, 1964; Fink and Shapiro, 1965) on an IBM 1710 computer system. With this method, EEG's were analyzed for a total of five minutes in the predrug period and up to sixty minutes after drug administration in thirty-second samples (periods of 1 to 2 seconds between each sample were not analyzed). The period analysis data were not used for statistical procedures because there were not enough artifact-free samples. A thirty-second sample size proved to be too long to obtain artifact-free samples after hallucinogenic drugs.

The subject's behavior was rated using a 70-point psychopathological rating scale (Itil and Keskiner, 1966) before and thirty minutes after administration of the hallucinogenic drugs. Ratings were also made thirty minutes after injection of chlorpromazine in those subjects who received this additional drug.

RESULTS

Clinical Changes

After LSD the subjects primarily experienced visual, colorful hallucinations; pleasurable, fantastic delusions with emotional involvement; agitation; and euphoric mood. The level of consciousness was not markedly altered. Three patients who had hallucinations and delusions prior to being given LSD had a decrease of these symptoms after the drug. In two subjects a drowsiness-like state was observed after LSD. Five patients did not present any major drug-induced behavior changes.

After Ditran, nine subjects demonstrated a confusional-delirious state with motor agitation; unpleasant hallucinations; loss of concentration; poor memory; disorientation; slurred, blocked, and incoherent speech; blocking and disruption of continuous thought process; disturbance in communication and contact; and marked fluctuations in the level of consciousness. Three patients demonstrated deep sleep and stuporlike states, and another three showed only slight behavioral alterations.

The psychological test results were also related to the particular drug given. After LSD, subjects could perform tasks and drawing tests, but these were uncoordinated and unrealistic. After Ditran, subjects were not able to perform any kind of tests and drawings were poor because of lack of concentration, memory, and motor ability.

EEG Changes

LSD in the dosage range of 0.001–0.002 mg/kg/5 min given intravenously induced an acceleration in all frequency bands, reduction of amplitude, and a decrease of synchronization and rhythmical activity (Fig. 5-1). The onset of EEG alterations was observed five to ten minutes after the injection, and the maximal changes occurred thirty minutes after LSD. The quantitative EEG analysis demonstrated that the alpha peak decreased as well as shifted gradually to a higher frequency (Fig. 5-2). Analog frequency analysis of the records of eighteen patients given LSD showed a significant increase (T-test, Sign test, Wilcoxon test) in high frequency bands (20, 22, 24, 27, 30, and 33 cps) thirty minutes after the injection in comparison to the mean values of the predrug EEG frequencies. Quantitative EEG analysis indicated that the EEG changes occurred after LSD in a group of five sub-

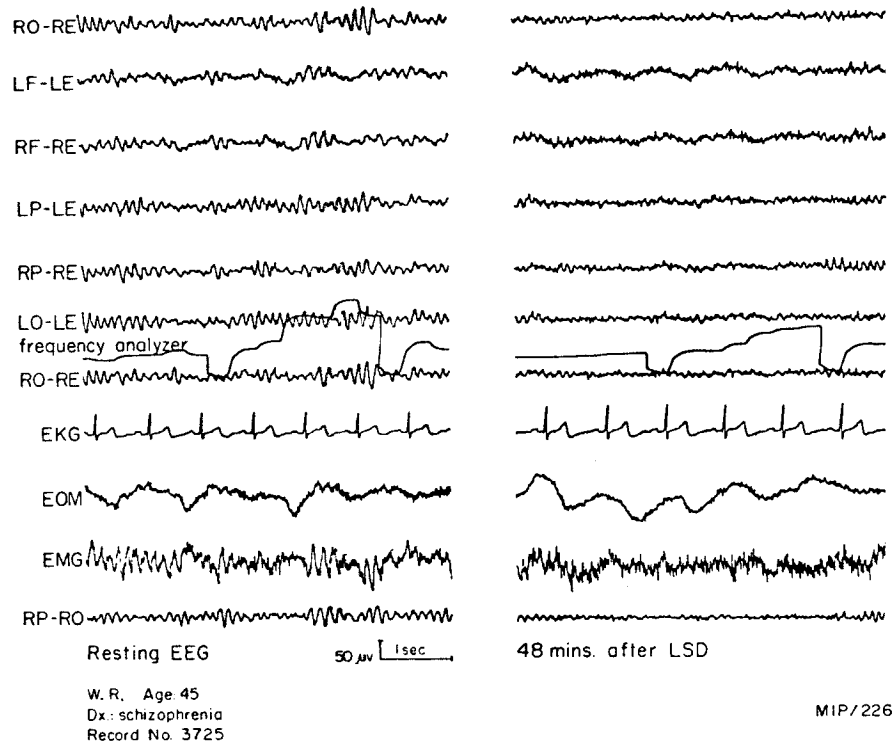

FIGURE 5-1. EEG changes after **LSD** (0.001 mg/kg I.V.). The EEG record, 48 minutes after LSD, illustrates the decrease of alpha activity, synchronization, and rhythmicity; flattening and acceleration of EEG with beta predominance; increase of muscle potential (*EMG* channel); bradycardia (*EKG* channel); no alteration of eye movements (*EOM* channel).

jects who exhibited major behavior changes. An increase of perceptual disturbances, thought disorder, and hyperagitation were associated with a decrease of the 8 to 10 cps band of alpha activity and an increase of 15 to 33 cps band of fast waves (Fig. 5-3). Patients who showed no marked clinical effects also did not demonstrate marked EEG changes after LSD.

Period analysis demonstrated that LSD induced marked alterations over a period of time, particularly in the 0 to 7.5 cps frequency bands (Fig. 5-4). Twenty minutes after the injection, the average frequency derived from the baseline cross analysis showed a significant increase over the predrug mean value. The average frequency deviation (frequency variability in the baseline cross analysis), the mean amplitude, and amplitude variability revealed no significant changes in comparison to predrug records until twenty minutes after the injection (Fig. 5-5). Period analysis data were not accurate enough to be analyzed twenty-five minutes after the injection because of marked artifact due to an increase of motor activity.

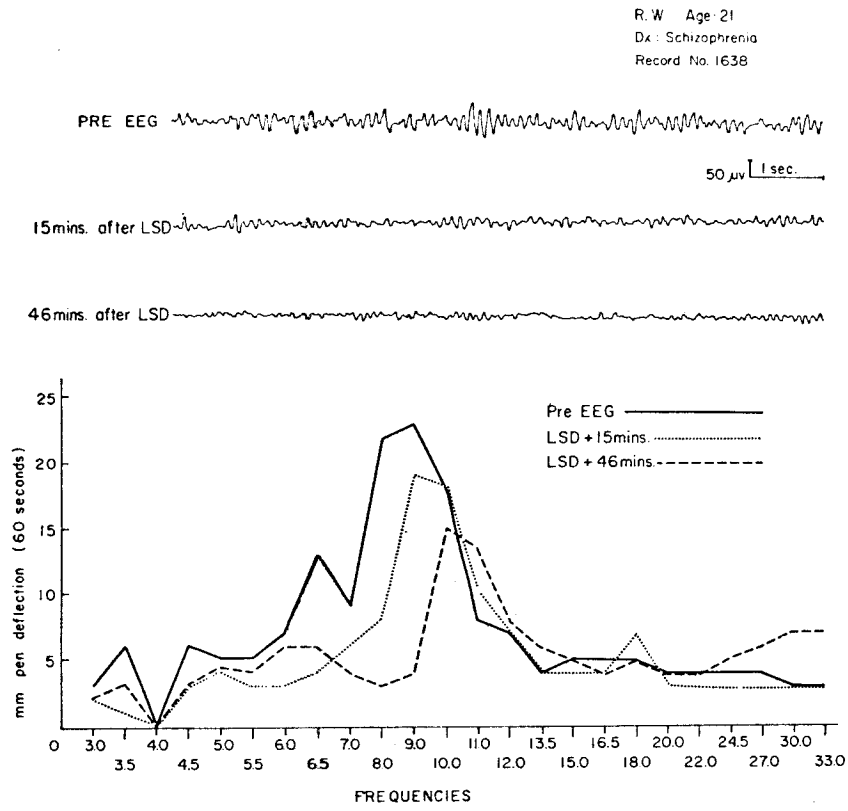

FIGURE 5-2. EEG changes after LSD (0.001 mg/kg IV) based on analog frequency analysis. The abscissa shows the EEG frequencies (0 to 33 cps) and the ordinate represents the pen deflection in millimeters recorded by the analyzer. Analysis of 60-second EEG samples indicates a decrease of electrical power (pen deflection) in 8 to 9 cps activity 15 minutes and 46 minutes after LSD in comparison to predrug values. Increase of 11 to 13.5 cps and 24.5 to 33 cps activity 46 minutes after LSD is also illustrated.

Ditran in the dosage range of 0.004–0.25 mg/kg/5 min given intravenously induced marked disorganization in the EEG with an increase of slow activity as well as very fast activity (Fig. 5-6). Analog frequency analysis clearly demonstrated a decrease of alpha and an increase of slow activity (Fig. 5-7). Drug-induced changes occurred immediately after the injection was completed and lasted up to twenty-four hours. Statistical evaluation (Sign test, Wilcoxon test, and T-test) from eighteen subjects revealed a significant increase of 4, 5, 6, and 7 cps frequencies thirty minutes after Ditran as compared to the predrug mean values.

While changes in alpha and delta bands could be shown with the analog frequency analyzer, the increase in beta activity, and alteration of other EEG

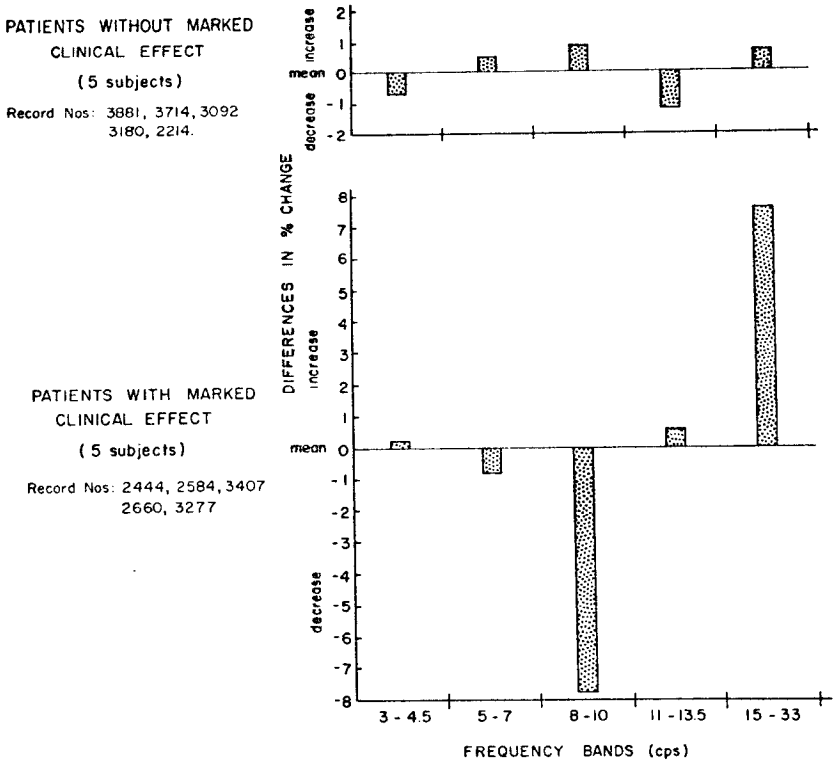

FIGURE 5-8. EEG changes after LSD (0.001 mg/kg IV) based on analog frequency analysis. Patients without marked clinical manifestations did not show significant changes in any of five frequency bands after LSD in comparison to predrug records (*upper panel*). Patients who demonstrated clinical changes also showed significant decrease of power in the 8 to 10 cps activity and a smaller increase in the 15 to 33 cps waves (*lower panel*). The increases and decreases (*ordinate*) refer to percentage changes in pen deflection as recorded by the analyzer at various frequencies (*abscissa*).

components could only be clearly demonstrated using period analysis. The average frequency, frequency variability, and mean amplitude increased markedly a few minutes after Ditran injection in comparison to predrug mean values (Fig. 5-8). Analysis of the single frequency bands showed an increase of slow activity (0 to 7.5 cps) and high frequency activity (above 26.6 cps). Alpha activity (7.5 to 13 cps) decreased. No significant changes in the 13 to 26.6 frequency bands were seen (Fig. 5-9).

As in the case of LSD, the analysis of the clinical data has shown a close correlation between behavior and EEG changes after Ditran. In patients with marked behavior alterations there were significantly more EEG changes than in subjects who did not exhibit major behavior changes.

Comparison of the effects of Ditran and LSD in the same group of patients showed that the drug-induced changes were significantly different. The frequency analyzer data from eighteen subjects demonstrated that Ditran induced more theta activity (6, 6.5, and 7 cps bands) than LSD, while a greater increase of fast beta activity (20, 22, 27, 30, and 33 cps bands) was seen after LSD (Sign test and Wilcoxon test).

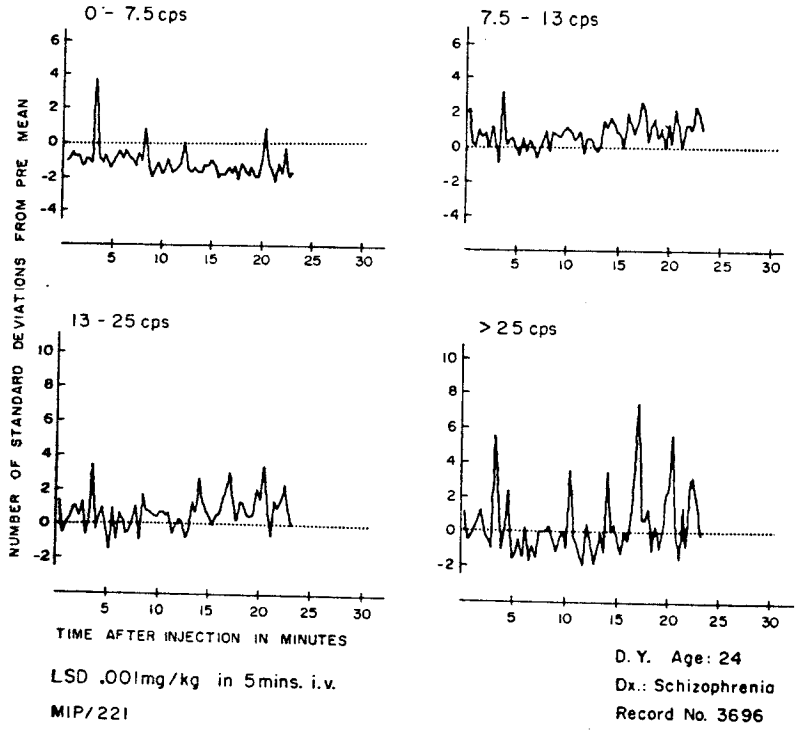

FIGURE 5-4. LSD response curves based on period analysis. Continuous decrease of 0 to 7.5 cps activity and slight increase of 13 to 25 cps waves after LSD in comparison to predrug mean values.

Drug Interaction

Differences in the effects of Ditran and LSD on the EEG and behavior could also be demonstrated when chlorpromazine was given after these drugs. After intravenous chlorpromazine administration, EEG changes induced by LSD were reversed: fast activity decreased, amplitude increased, and the alpha activity was present again; altogether, the EEG pattern became similar to the pre-LSD record. The antagonistic effect of chlorpromazine on the EEG changes induced by LSD could also be demonstrated by quantitative analysis (Fig. 5-10). This reversal effect was seen in behavior altera-

tions as well: psychomotor agitation induced by LSD was suppressed by chlorpromazine.

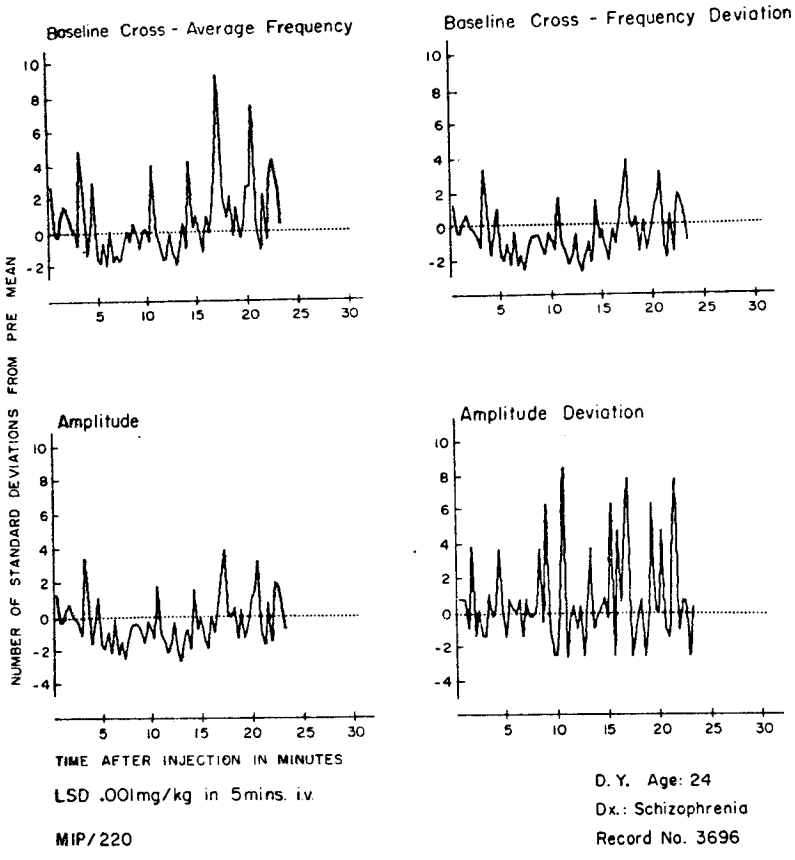

FIGURE 5-5. LSD response curves based on period analysis. Baseline cross average frequency showed a significant increase 20 minutes after LSD injection in comparison to predrug mean value. There were no significant changes in other EEG characteristics until 25 minutes after injection.

Chlorpromazine interaction with Ditran was different from that with LSD. The very small dosages of chlorpromazine given intravenously thirty to sixty minutes after Ditran administration rapidy potentiated Ditran-induced slow waves and decreased fast activity. The EEG showed a deep sleeplike pattern with high voltage slow waves and some 8 to 14 cps spindle activity. The increase of slow waves and decrease of fast activity could also be seen with quantitative EEG analysis (Fig. 5-11). The confusional-delirious syndrome associated with Ditran was also altered with chlorpromazine. Motor agitation was reduced, consciousness changes were increased, and patients demonstrated a comalike state.

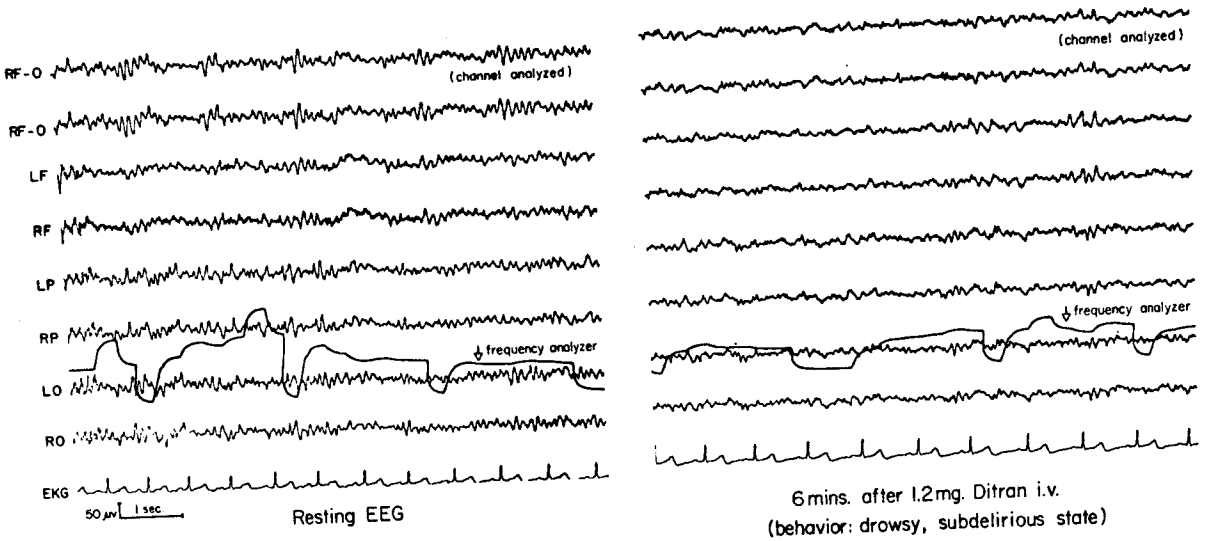

FIGURE 5-6. Ditran (0.02 mg/kg I.V.) induced disorganization of the EEG. Decrease of alpha activity, synchronization, and amplitude and increase of slow waves and superimposed fast beta activity 6 minutes after Ditran (cf. Fig. 5-1 for further explanation of the recordings.)

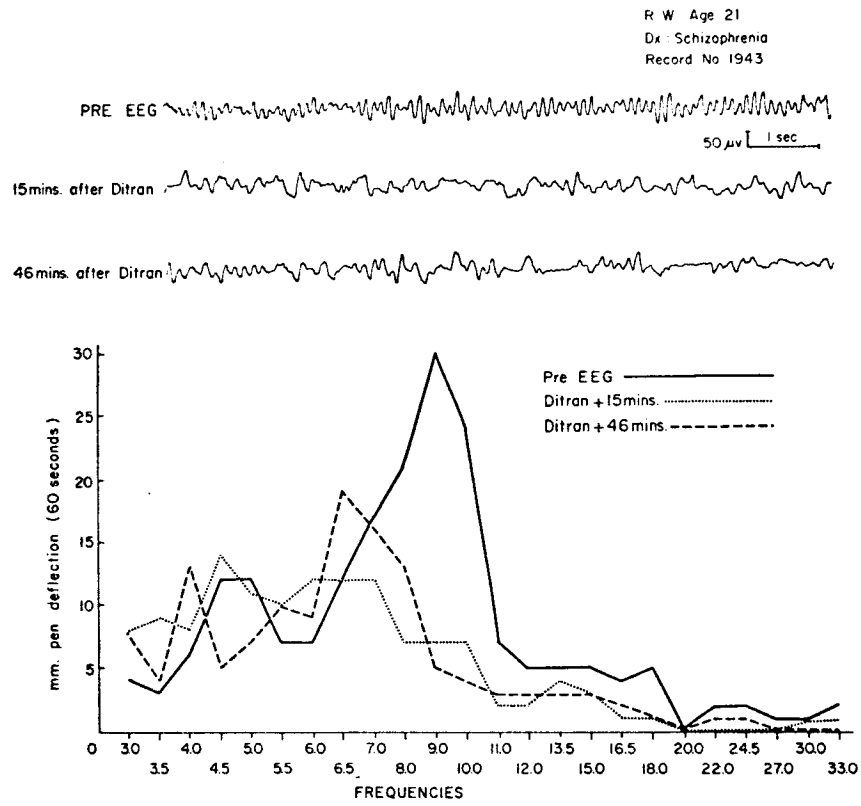

FIGURE 5-7. EEG changes after Ditran (0.05 mg/kg IV) based on analog frequency analysis. Decrease of the power in 9 to 10 cps frequency bands 15 and 46 minutes after Ditran with increase of 6 to 7 and 3 to 4 cps activity (*lower panel*). The representative EEG recordings shown above.

DISCUSSION

Various studies have shown that LSD produces characteristic EEG alterations in normal subjects (Rinkel *et al.*, 1952; Gastaut *et al.*, 1953; Bradley *et al.*, 1953; Elkes *et al.*, 1954). In psychiatric populations, however, minimal or no changes were reported (Forrer and Goldner, 1951; Anderson and Rawnsley, 1954). The present study demonstrated that significant alterations may be also seen after LSD in a group of chronic schizophrenic patients provided the EEG is analyzed quantitatively. In some patients, however, no noticeable EEG changes were observed. This may be related to the predrug resting EEG pattern, as all of these patients had slow resting records. As previously reported from this laboratory, patients with slow EEG's (epileptics, patients with tumors, or after ECT or psychotropic drugs) showed much less response to LSD than patients with predominant alpha activity

(Bente *et al.*, 1958). In recent investigations it was observed that some of the so-called therapy-resistant schizophrenic patients with "hypernormal EEG's" (high voltage slow alpha records with hypersynchronization and rhythmic patterns) do not exhibit clinical and EEG changes in spite of very high dosage (680 μg) intravenous LSD administration (Itil, 1968).

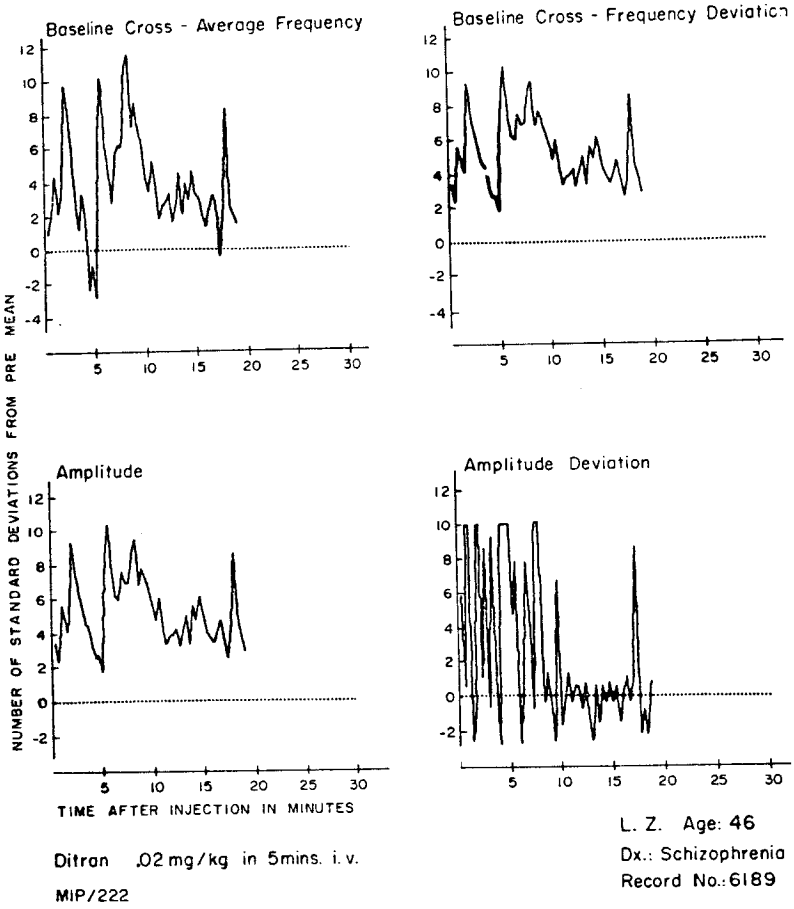

FIGURE 5-8. Ditran response curves based on period analysis. Increase of average frequency, frequency deviation, and amplitude a few minutes after Ditran administration in comparison to predrug values. Artifact is responsible for changes in amplitude deviation.

The present investigations with Ditran corroborate previous reports of a close correlation between behavior and EEG changes (Flügel and Itil, 1962; Itil, 1964 and 1966; Wilson and Shagass, 1964; Itil and Fink, 1966 and 1968). On the other hand, this relationship between EEG changes and behavior is not always seen as in the case of the "dissociation" of EEG and behavior

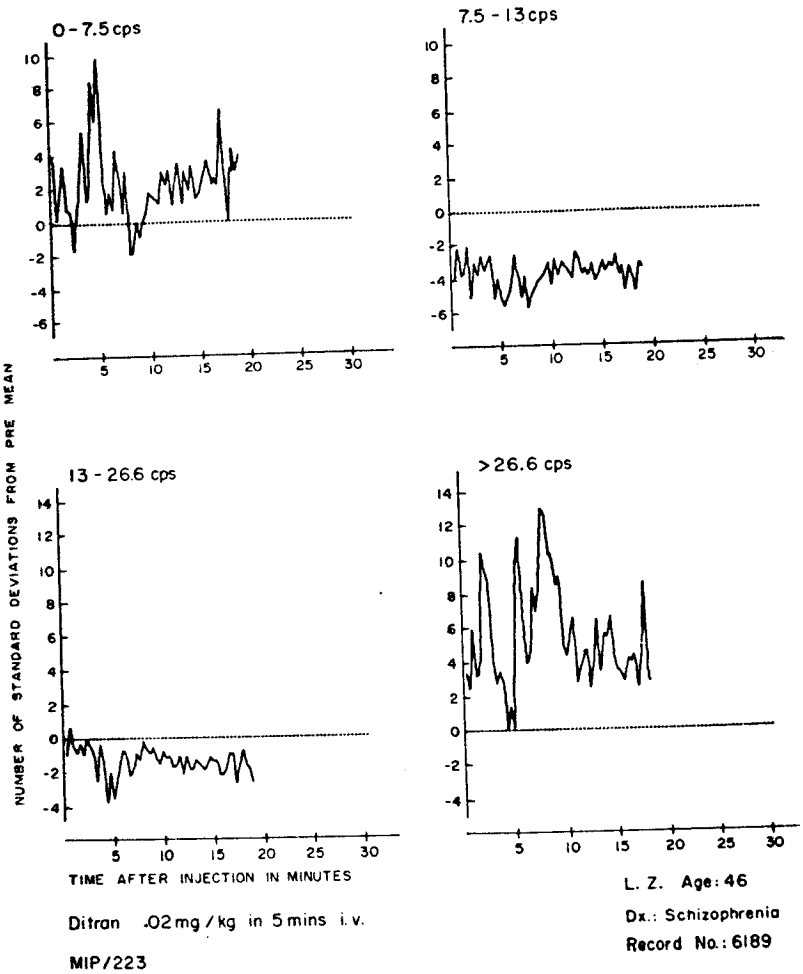

FIGURE 5-9. Ditran response curves based on period analysis. Increase of 0 to 7.5 cps as well as 26.6 to 40 cps activity and a decrease of 7.5 to 13 cps activity is indicated immediately after Ditran administration in comparison to predrug mean values.

after anticholinergic drugs described by Wikler (1952) and Bradley and Elkes (1953) in animals.*

*However, this difference between man and nonhuman species may not be supported by newer data. While a degree of "divorce" or "dissociation" was described by Bradley and Elkes (1953) and Wikler (1952) who used the available at that time, less sophisticated EEG evaluation methods, currently the EEG and the behavioral action of cholinergic and anticholinergic agents appeared more correlatable. This is also partially due to the present better understanding of the EEG-behavior relationship and to a more precise differentiation of various EEG and behavioral states. Thus, cholinergically-induced EEG alerting may be correlatable with paradoxical sleep rather than referred to as a "divorce phenomenon" (cf. Karczmar, in *Principles of Psychopharmacology*. W. Clark, Ed., Academic Press, 1969, (in press). [Editorial Comment.]

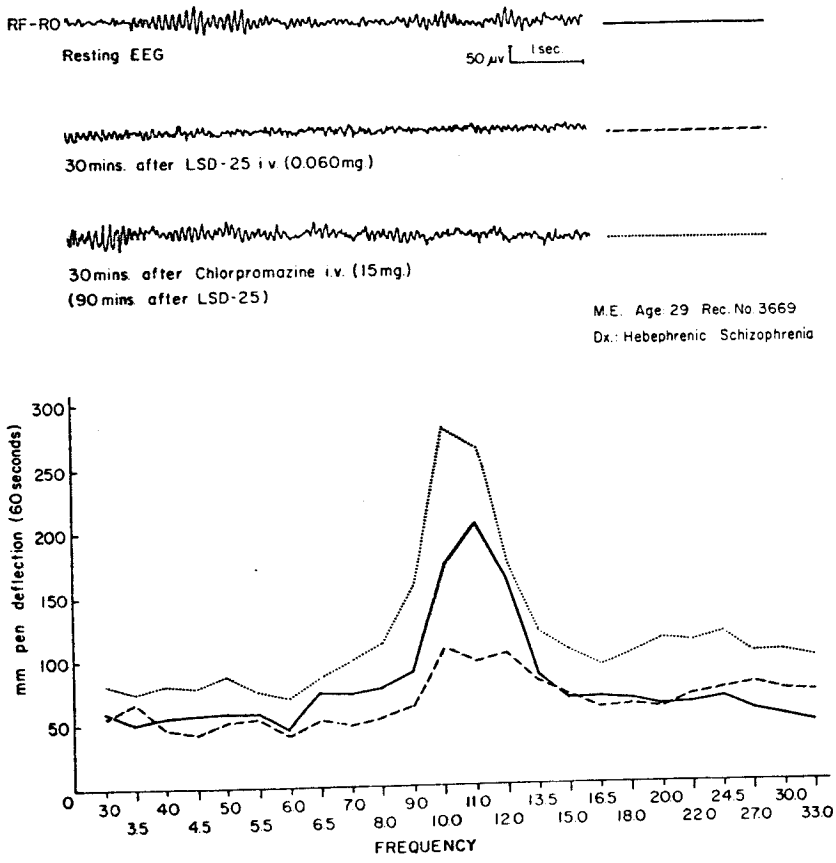

FIGURE 5-10. EEG changes after LSD and following administration of chlorpromazine based on analog frequency analysis. Marked decrease of alpha activity and decrease of power in alpha bands 30 minutes after LSD (compare the two top EEG records). The behavioral correlate consisted of an increase of psychomotor agitation. Thirty minutes after chlorpromazine was given (90 minutes after LSD injection) alpha activity reoccurred even more strongly than in pre-LSD records (third EEG record). The increase of power in alpha frequency was seen by quantitative analysis (*lower panel*). The behavioral correlate consisted of a decrease of psychomotor agitation.

It is obvious from the quantitative study of EEG changes and the clinical findings that LSD and Ditran have different modes of action, as Wilson and Shagass (1964) have noted on the basis of their evoked potential and behavior investigations. Both drugs produce EEG desynchronization. LSD commonly induces acceleration, whereas Ditran is characterized by an increase of both slow and fast activity. Both drugs increase psychomotor activity. Hallucinatory phenomena occurs predominantly after LSD, while consciousness changes are most characteristic of Ditran. The differences in EEG and behavior alterations after either drug are clearly seen in their inter-

action with chlorpromazine. Chlorpromazine reversed psychomotor activity induced by LSD without any visible consciousness changes, while chlorpromazine given after Ditran produced a coma-like state. This state was associated with a marked increase of slow waves in the EEG.

According to our findings, a close correlation between EEG and behavior changes can be found in man both after the indole hallucinogen LSD and the anticholinergic hallucinogen Ditran when quantitative methods are employed.

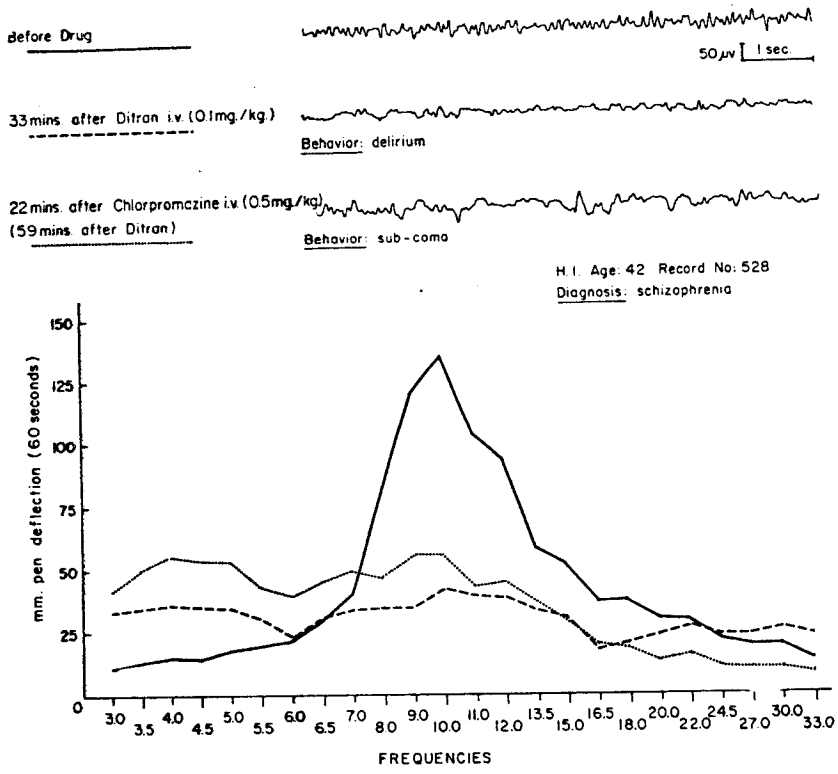

FIGURE 5-11. EEG changes after Ditran and following administration of chlorpromazine based on analog frequency analysis. Decrease of alpha activity in EEG and increase in slow waves 33 minutes after Ditran. Decrease of power in alpha frequency and increase in slow frequency bands (compare the two top EEG records). The behavioral correlate: delirium. Twenty-two minutes after chlorpromazine injection, slow activity was potentiated and fast activity decreased (lowest EEG record). The increase of power in slow frequency and decrease in fast bands (quantitative analysis) is shown in the lowest panel. The behavioral correlate: subcoma.

SUMMARY

Behavior and EEG changes were studied after intravenous administrations of LSD and Ditran in a group of chronic schizophrenic patients. Be-

havior was rated using psychopathological rating scales, and the EEG was analyzed quantitatively by computer methods and analog frequency analysis. The evaluation of the eighteen LSD and eighteen Ditran experiments showed that both drugs increased fast activity in the EEG (LSD more than Ditran) and that Ditran produced additional slow waves. LSD increased motor agitation and hallucinations, while Ditran decreased the level of consciousness and induced less hallucinatory activity. The differences between the two hallucinogenic drugs were more prominent when chlorpromazine was given after these compounds. With chlorpromazine, the clinical and EEG alterations induced by LSD were reversed. Chlorpromazine, when given after Ditran, produced a coma-like state with marked slow activity. In some patients neither drug produced clinical or EEG changes; in others, preexisting psychopathology was suppressed by both drugs. The notion of a "dissociation" of EEG and behavior after anticholinergic drugs could not be substantiated in our investigations. Close correlations between EEG changes and alterations in psychopathology were seen after LSD as well as after the anticholinergic Ditran.

Acknowledgments

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