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The Use of LSD and Ditran in the Treatment of Therapy Resistant Schizophrenics

(Symptom Provocation Approach)

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While many schizophrenic patients improve with psychotropic drug treatment, there are others who exhibit neither a favorable therapeutic response nor any significant behavior changes in spite of long periods of intensive treatment. These patients have been called "therapy resistant"[4,5,8]. There is no general agreement on the etiology or nosology of this group of patients. It is accepted, however, that the majority demonstrate a blunt and adynamic course without frequent florid psychotic episodes[20].

In our previous studies it was observed that most of the therapy resistant schizophrenics have electroencephalograms (EEG) characterized by predominant slow alpha activity and synchronization, so-called "hypersynchronous" or "hypernormal" EEG's[8,11,13,16]. The EEG patterns of such patients showed no significant alterations during chronic treatment with psychotropic drugs and were therefore said to be "hyperstable"[17]. It was hypothesized that "hyperstability" of the EEG might be an indicator of "therapy resistance." If so, the patients should become more responsive to psychotropic drug treatment once the stable, hypersynchronous EEG pattern has been altered[12,13]. LSD and Ditran have been suggested for this purpose[13] since both compounds induce desynchronization and disorganization in the EEG[1-3,7,9,14] The present report is the result of an open pilot trial to evaluate our hypothesis.

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Material and Method

Eighty-five chronic schizophrenic patients without clinically manifest organic disorders were selected from various state hospitals. Each patient had a history of a minimum of 3 years psychiatric illness and had been continuously hospitalized since the last admission for a minimum period of 1 year. All of them had been refractory to various psychosomatic treatments and were considered "therapy resistant". Following an initial observation and investigation period, all patients underwent intensive treatment with conventional psychotropic drugs (doctor's choice) for a period of 2 to 12 months, the average being 9 months (period I), (Fig. 1). Twenty-seven showed enough improvement to meet the criteria for psychiatric dischargeability and were released from the hospital. Fifty-one of the remaining fifty-eight "real" resistant patients were selected on the basis of their EEG patterns for "unconventional" treatment procedures. These included patients with hypersynchronous patterns, epileptic activity, slow dysrhythmic patterns or low voltage fast activity. First, each patient received a placebo medication for a period of 2 to 16 weeks (period II). Following this, seventeen patients were treated with hallucinogenic drugs (period III). Of these, nine patients with predominantly hypersynchronized alpha EEG's were given LSD, and eight patients with predominantly rhythmical patterns and/or slow activity were treated with Ditran. Both hallucinogenics were administered intravenously in the EEG laboratory under controlled conditions. The number of injections ranged from 4-15 per patient and the dosage varied from 0.005-0.84 mg. for LSD and 1-21 mg. for Ditran. Because tolerance to these drugs develops

early, there was a 1 to 2 week interval between each administration, the dosage being progressively increased. Treatment with hallucinogenics was continued for a minimum of 3 weeks and terminated on the basis of the alterations of the EEG and/or behavior pattern. As soon as the EEG pattern was accelerated and desynchronized or the behavior had markedly deteriorated, the hallucinogenic was discontinued and the doctor's choice of psychotropic drug treatment was initiated and continued for a period of 2 to 12 months (period IV). Hallucinogenics were discontinued after a maximum of 3 months treatment in patients in whom no EEG or behavior alterations were observed and conventional drug treatment was resumed. Six out of the nine *LSD-treated* and six out of the eight *Ditran-treated* patients completed the four study periods. These patients had a history of psychiatric hospitalization extending from 5 to 21 years, with an average of 11 years; they had been continuously hospitalized since their last admission for 1 to 16 years, with an average of 5.5 years. Their ages ranged from 25 to 48 years, with an average of 36 years. Four were diagnosed as paranoid, two hebephrenic, and six chronic undifferentiated type of schizophrenia. Each patient was evaluated at bi-monthly intervals during the total study period, using a psychopathological rating scale covering 70 symptoms in 11 clusters[15]. A 7-point rating scale (which ranged from 1 = normal to 7 = extremely ill) was used for the global evaluation. The scores of the last rating made at the end of each of the four treatment periods were used for the statistical analysis. At least two resting EEG's were recorded for each patient during the various study periods. Visual assessment of the four records of each patient (one record from each treatment period) was used for the statistical procedures. Visual analysis included 14 single EEG measurements such as percentage of alpha, beta, theta and delta activities; absolute amplitude; monolateral and bilateral rhythmical patterns; bilateral synchronization; frontal to occipital synchronization; spikes; sharp waves; burst activity; paroxysmal dysrhythmic pattern; and sleep-like activity. The clinical and EEG evaluations were made independent of each other.

Clinical Results

The global clinical evaluation scores of the *LSD-treated* patients at the end of each study period are shown in Table I. All patients were

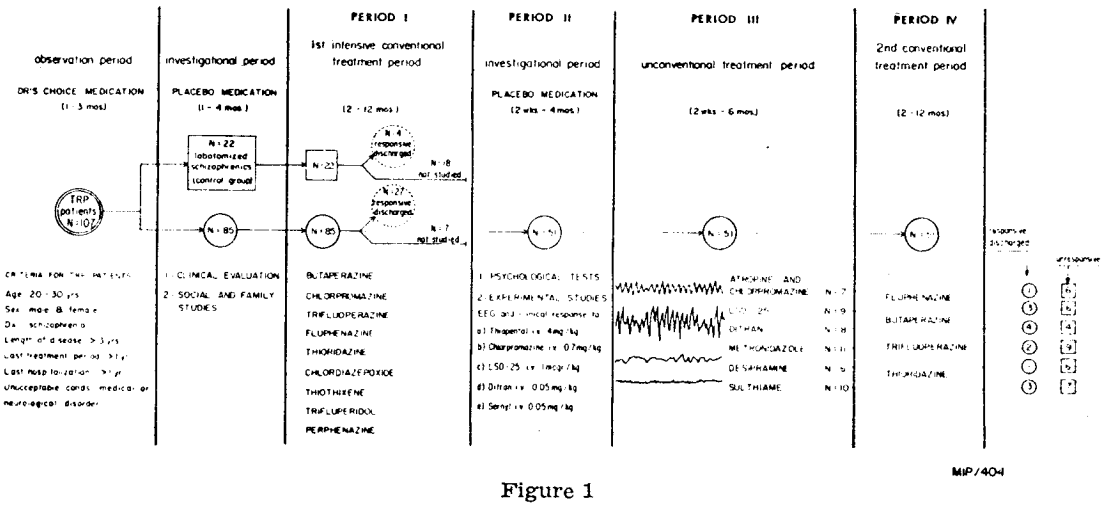

Figure 1

TABLE I

GLOBAL EVALUATION SCORES* OF LSD-25 TREATED GROUP

(N: 6)

	Treatment Periods				
Patient	I	II	III	IV	Outcome
1. P.F.	4	4	4	2	Discharged
2. L.G.	4	5	6	2	Discharged
3. M.H.	6	6	7	5	
4. G.McN.	3	5	6	2	Discharged
5. M.L.M.	6	6	7	6	
6. M.S.	6	7	7	4	

Two way analysis of variance "F test" of 11 symptom clusters between the 4 periods: III > II > I > IV at .01 level or better.

*Code: 1 = Normal, not at all, 2 = Borderline mentally ill, 3 = Mildly ill, 4 = Moderately ill, 5 = Markedly ill, 6 = Severely ill, 7 = Among the most extremely ill

TABLE II

GLOBAL EVALUATION SCORES* OF DITRAN TREATED GROUP

(N: 6)

	Treatment Periods				
Patient	I	II	III	IV	Outcome
1. K.D.	5	5	6	4	
2. J.F.	5	5	6	4	
3. H.I.	4	5	7	3	Discharged
4. M.M.	4	5	7	2	Discharged
5. E.S.	5	5	5	2	Discharged
6. H.T.	4	5	5	2	Discharged

Two way analysis of variance "F test" of 11 symptom clusters between the 4 periods: III > II > I > IV at .01 level or better.

*Code: 1 = Normal, not at all, 2 = Borderline mentally ill, 3 = Mildly ill, 4 = Moderately ill, 5 = Markedly ill, 6 = Severely ill, 7 = Among the most extremely ill

moderately to severely psychotic during the first doctor's choice drug treatment period (period I). These scores remained the same or increased slightly during the placebo period (period II). An exacerbation of the symptomatology was observed during the subsequent LSD treatment (period III). On the other hand, there was a marked decrease of the scores during the second doctor's choice drug treatment period (period IV). Three of the six patients showed marked remission and were released from the hospital. In two of the remaining three patients, although the psychotic symptomatology decreased in comparison to the previous doctor's choice treatment period, the improvement was not sufficient for rehabilitation. A two-way analysis of the variance of the 11 symptom clusters of 70 individual symptoms showed that each period significantly differed from the other ($P<.01$). The greatest deterioration occurred during LSD treatment (period III). This was seen particularly in the symptoms of depersonalization, perceptual and thought disturbance and disturbed motor behavior. The most improvement occurred after LSD in the second doctor's choice drug treatment period (period IV). The symptom clusters of higher mental functions (attention and concentration, comprehension, insight and judgment) and of general attitude (negativism,

TABLE III

EEG CHANGES DURING VARIOUS TREATMENT PERIODS OF THE LSD TREATED PATIENTS (ANALYSIS OF VARIANCE)

N: 6

EEG Measures / Periods	Alpha Activity	Bilateral Rhythmical Pattern	Frontal - Occipital Synchronization
I vs. II		++	+
I vs. III	++	++	
I vs. IV	--		-
II vs. III			
II vs. IV	--	--	--
III vs. IV	--	--	--
Comparison of the periods	IV > I > II > III	IV > I > II > III	IV > I > II > III

Treatment Periods:

- decrease sig. < .05 level
-- decrease sig. < .01 level
+ increase sig. < .05 level
++ increase sig. < .01 level

I: Dr's. Choice Medication (First)
II: Placebo Treatment
III: LSD Treatment
IV: Dr's Choice Treatment (Second)

COMPARISON OF IMPROVED (N:3) AND UNIMPROVED (N:3) PATIENTS

Increase of Beta Activity	:	Improved Group > Unimproved Group	(< .01)
Amplitude	:	Improved Group > Unimproved Group	(< .01)
Increase of Monopolar Rhythmical Pattern	:	Improved Group < Unimproved Group	(< .01)

aggressive behavior, withdrawn and asocial attitude and uncooperativeness) were significantly improved in this period.

The overall global evaluation scores of the *Ditran-treated* group at the end of each treatment period are shown in Table II. The patients in this group were moderately to markedly psychotic at the end of the first doctor's choice drug treatment (period I). During placebo treatment (period II) the scores of three patients increased. Psychopathology scores further increased in all but two patients during Ditran treatment (period III). There was an overall marked decrease in the scores of all of the patients in the second doctor's choice psychotropic drug treatment period (period IV).

TABLE IV

EEG CHANGES DURING VARIOUS TREATMENT PERIODS OF THE DITRAN TREATED PATIENTS (ANALYSIS OF VARIANCE)

N: 6

EEG Measures / Periods	Monopolar Rhythmical Pattern
I vs. II	
I vs. III	++
I vs. IV	--
II vs. III	++
II vs. IV	--
III vs. IV	--
Comparison of the periods	IV > II > I > III

Treatment Periods:

-	decrease sig. < .05 level	I	:	Dr's. Choice Medication (First)
--	decrease sig. < .01 level	II	:	Placebo Treatment
+	increase sig. < .05 level	III	:	Ditran Treatment
++	increase sig. < .01 level	IV	:	Dr's. Choice Medication (Second)

COMPARISON OF IMPROVED (N:4) AND UNIMPROVED (N:2) PATIENTS

Increase of Theta Activity	:	Improved Group < Unimproved Group	(< .05)
Increase of Amplitude	:	Improved Group > Unimproved Group	(< .05)
Increase of Frontal-Occipital Synchronization	:	Improved Group > Unimproved Group	(< .05)
Increase of Burst Activity	:	Improved Group > Unimproved Group	(< .05)

Four of the six patients had shown sufficient improvement to be released from the hospital. The two remaining patients' clinical state also showed some improvement in comparison to the previous conventional treatment period, but they still required hospital care. Analysis of the variance of the 11 symptom clusters of the 70 individual symptoms showed that each period significantly differed from the other ($P<.01$). The deterioration of the symptomatology was more evident during Ditran treatment (period III), with the greatest changes occurring in the symptom clusters of affect (inappropriateness and lability), mood, thought process (blocking, irrelevance and disorganization of thinking), orientation, consciousness, and motor behavior. The highest level of improvement was seen during the second doctor's choice drug treatment period (period IV) following the Ditran treatment period. The symptom clusters of higher mental functions, orientation, general attitude, motor behavior, affect and thought process significantly improved ($P<.01$).

EEG Results

Four of the *LSD-treated* group of patients had predominant alpha records (more than 50%) and two patients had mixed EEG's with beta, alpha, theta and delta activity. Three of the patients with alpha EEG's also had secondary theta and delta waves. Statistical analysis of the data (analysis of variance) demonstrated that three of the fourteen EEG measurements i.e., alpha activity, bilateral rhythmical patterns and frontal to occipital synchronization, were significantly altered in the *LSD-treated* group of patients during all four treatment periods (Table III). Bilateral rhythmical patterns and frontal to occipital synchronization were more prominent during the first pe-

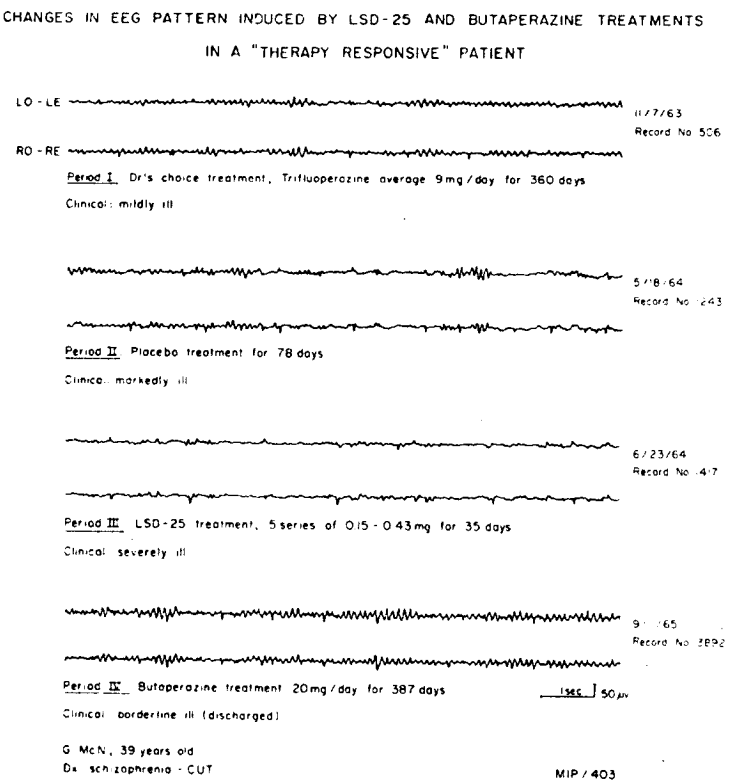

Figure 2

riod of doctor's choice medication (period I) than they were during placebo medication (period II), while the percentage of alpha activity and bilateral synchronization during LSD treatment (period III) was significantly decreased in relation to that occurring during the first period of doctor's choice medication (period I). All three EEG characteristics (alpha activity, rhythmical patterns and synchronization) during the second doctor's choice treatment period (period IV) showed a significant increase over the placebo (period II) and LSD treatment periods (period III). Significant differences in these EEG variables could be observed in the four treatment periods. The maximum amount of alpha activity, rhythmicity and synchronization were found during the second period of doctor's choice treatment, (period IV) whereas the minimum amount was observed during the LSD treatment period. The group of patients who demonstrated clinical improvement had more beta activity, higher amplitude and less monolateral rhythmical patterns during the placebo and LSD treatment periods than did those patients who did not improve.

Patients who showed marked EEG alterations during the second period of doctor's choice treatment, (period IV) in comparison to the placebo and LSD periods, also showed a high degree of improvement (Fig. 2). In contrast, patients who showed no significant improvement did not exhibit any significant EEG changes (Fig. 3).

Of *Ditran-treated* patients, two had predominantly alpha records, two theta and delta records and two mixed EEG's with alpha, theta, delta and beta activity. According to the statistical analysis of the data, only one (monolateral rhythmical pattern) of the 14 EEG

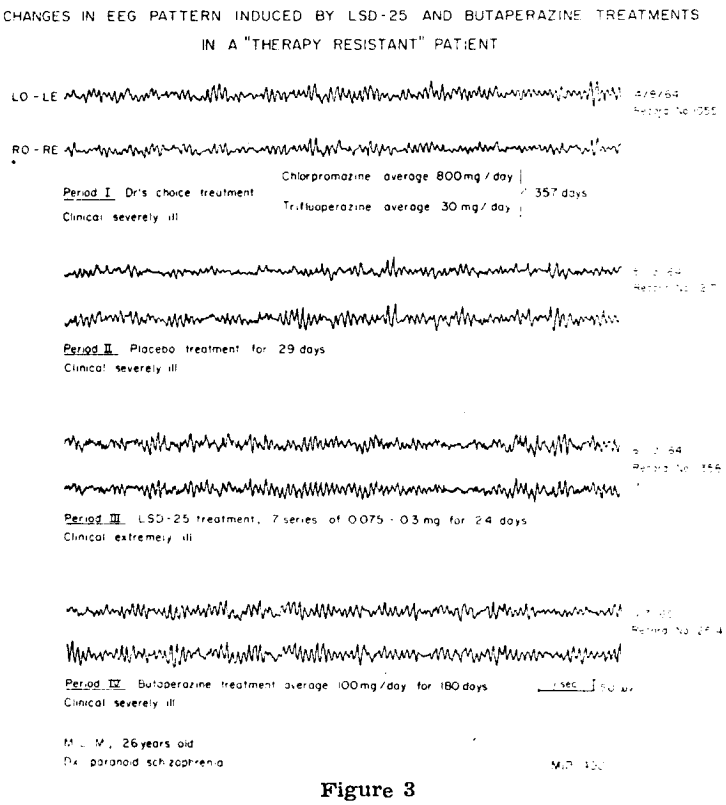

Figure 3

measurements was significantly altered in all four treatment periods (Table IV). The maximum rhythmicity was found during the second doctor's choice drug treatment period (period IV) and the minimum was observed during Ditran treatment (period III). The comparison of the EEG alterations with respect to prognosis showed that the improved patients, in contrast to the unimproved patients, had a smaller increase of theta activity, augmented amplitude, and a greater increase of synchronization and burst activity during the second period of doctor's choice drug treatment as compared to the placebo and Ditran treatment periods. Patients who showed marked clinical improvement demonstrated marked EEG changes (Fig. 4) while patients with no significant behavior alterations exhibited no appreciable EEG changes (Fig. 5).

Discussion

After altering the electroencephalographic pattern with LSD and Ditran, seven of twelve therapy resistant patients became more responsive to conventional drug treatment. Concurrent with EEG changes, both hallucinogenics temporarily activated psychotic symptomatology. LSD primarily exaggerated perceptual disturbances, disorders of thought content and thought process. Ditran activated the symptoms related to mood, affect and consciousness. The clinical deterioration with hallucinogenics was more evident in those patients who responded to subsequent psychotropic drugs. The EEG alterations were also more marked in these patients than in those who remained resistant.

The treatment of schizophrenic patients through symptom provocation is a relatively

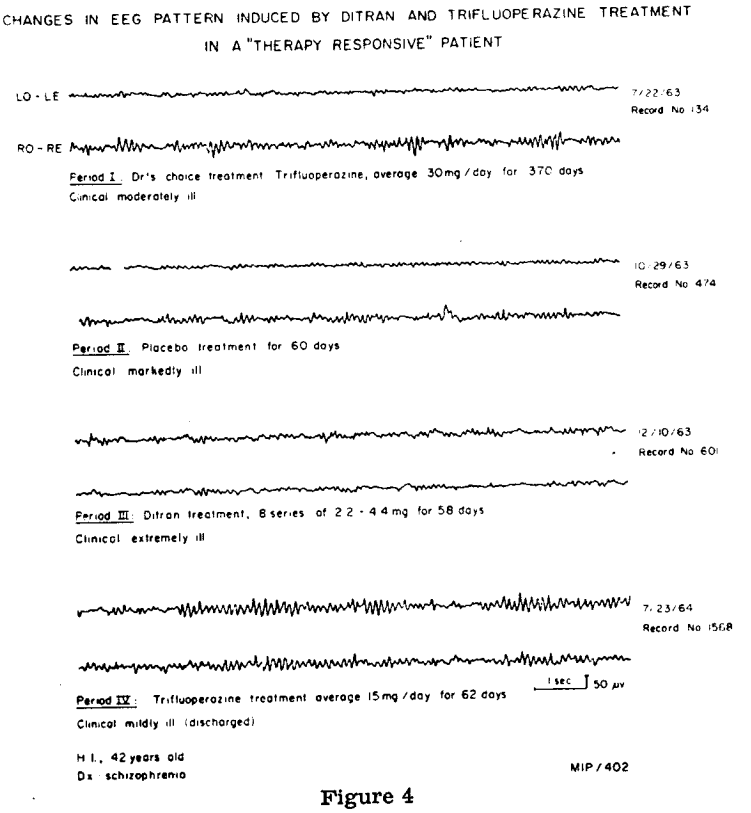

Figure 4

new approach[10]. This method was based on the clinical observations that some chronic schizophrenic patients exhibit remissions after an acute crisis. A sudden clinical improvement after high fever, infectious disease, or acute toxic confusional-delirious state has been observed in patients with long-term catatonic stupor. In these cases an exacerbation of the psychotic symptomatology preceded improvement. Various psychoactive drugs such as energizers, hallucinogenics and thymoleptics have been suggested for symptom provocation[6,10,13]. Although remarkable results have been reported in some patients, the superiority of this approach in comparison to conventional drug treatment has not yet been demonstrated.

We have partially achieved desynchronization of the stabilized hypersynchronous EEG pattern. Activation of the psychopathology was also observed to accompany desynchronization. But no spontaneous remission of the psychosis followed the symptom provocation. The psychopathology did improve, however, upon subsequent psychotropic drug treatment. The modification of behavior was correlated with the alteration of the EEG pattern (in the direction of synchronization).

Our results have limited significance because of the small number of subjects and the lack of a control group. Nevertheless, the fact that the selected patients were resistant and unresponsive to the first period of intensive psychotropic drug treatment, yet improved enough to be discharged from the hospital after the second period of psychotropic drug treatment following symptom provocation indicates that this is a valuable approach to the treatment of some resistant schizophrenics.

Whether the failure to respond to conventional drug treatment is related to the lack of "positive symptoms"[18], the absence of "psychic tension"[19] or "stable" consciousness and

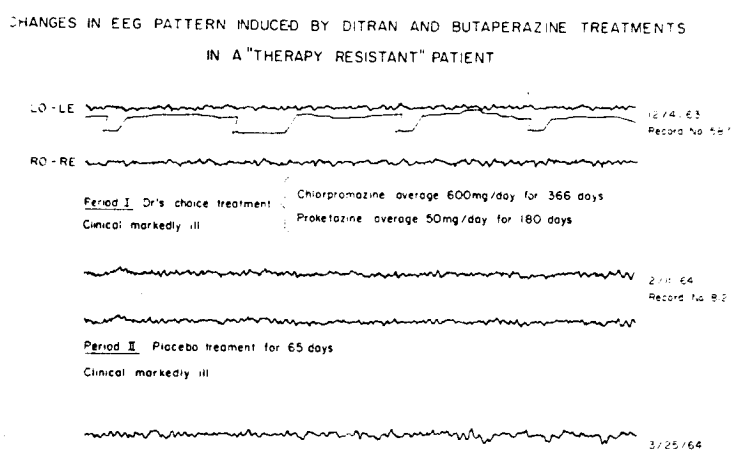

Figure 5

vigilance[21] in some patients cannot be answered without further investigations.

Summary

A group of chronic schizophrenic patients who did not show adequate response to drug treatment, were selected as "therapy resistant" and studied clinically and electroencephalographically. Based on the hypothesis that patients who do not respond well to drug treatment also fail to exhibit significant EEG changes, resistant patients were given "unconventional" drugs such as LSD and Ditran for a period of 1 to 3 months. The aim was to determine if by altering "stable" hypersynchronous EEG patterns in these patients the prognosis could be influenced. As soon as the EEG's were desynchronized, the patients were again treated with conventional drugs which had not been effective previously. It was observed that EEG desynchronization was accompanied by activation of psychotic symptomatology. The patients then became more responsive to the usual psychotropic drugs. Statistical analysis of the data indicated that patients who exhibited marked EEG changes after hallucinogenic drugs responded best to subsequent conventional treatment.

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