REGULAR ARTICLES

Clinical CEEG/DBM Findings with a New Antidepressant: Dothiepin

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Abstract. *Dothiepin hydrochloride, a new tricyclic antidepressant with a similar chemical structure to doxepin, was studied in a group of patients with major depressive disorder. This was a double-blind, placebo, and active drug (doxepin) controlled, parallel group study of 9 weeks duration. It was established that both dothiepin and doxepin produced statistically significant improvement compared to placebo. The therapeutic effect of dothiepin seems to be slightly better with less side effects than that of doxepin, but without a statistical evidence. CEEG/brain mapping data indicated that dothiepin has in most of the patients homogenous antidepressant type central nervous system (CNS) effects with secondary anxiolytic properties, whereas doxepin produces predominantly anxiolytic and secondary antidepressant effects. A linear correlation was demonstrated between the quality and quantity of CNS effects of first Test-Dose of drugs and therapeutic response after 9 weeks treatment. The subjects who showed most antidepressantlike CEEG response (profile) to Test-Dose drugs, also showed the best chronic, multiple dose treatment response.*

The CEEG profiles of both treatment responder and nonresponder patients, before treatment, were similar to each other and to our data base major depressive population. After antidepressant treatment, however, therapy responders showed significant change in CEEG profiles (increase similarity to normals) whereas nonresponders showed almost no change in CEEG profiles. This study suggests that quantitative EEG after test dose could be a biological predictor for treatment outcome in depression. A WHO-supported multicenter study is being conducted to test this hypothesis.

Key Words: dothiepin hydrochloride, doxepin, antidepressant, anxiolytic, CEEG, brain mapping, clinical EEG correlation, therapy responders, Test-Dose, biological predictor

Introduction

Prothiaden® (dothiepin hydrochloride)* is a tricyclic antidepressant with a chemical structure similar to that of doxepin. The difference is that it possesses a sulfur atom rather than an oxygen atom in the central ring (Figure 1).

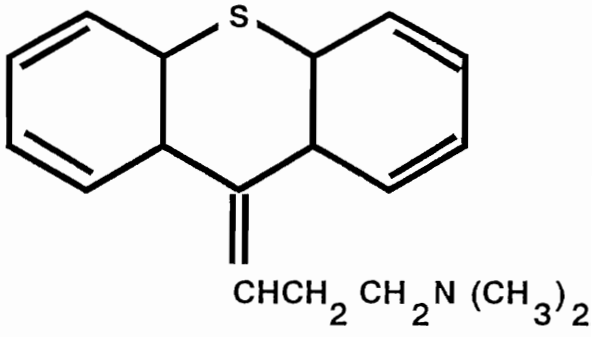

Figure 1. The Chemical Structure of Dothiepin.

As with other tricyclics, dothiepin and its major metabolites inhibit norepinephrine, and to a lesser extent, serotonin and dopamine reuptake in vitro models (Lancaster and Gonzalez, 1989).

Dothiepin significantly reduces strychnine-induced convulsions and toxicity (Boots, data on file). In a study of electroencephalographic changes in rabbits with implanted cortical and subcortical electrodes, dothiepin exerted a significant effect in antagonizing physostigmine-induced theta activity in the regions of the hippocampus and thalamus (Boots, data on file).

Clinical experience with dothiepin has been going on for over two decades (Lancaster and Gonzalez, 1989). An earlier study carried out in the United States compared dothiepin, placebo, and amitriptyline in 634 patients with major depressive disorder (Boots, data on file). The results of the study indicated that dothiepin was significantly superior to placebo with respect to improvements in cognitive disturbance, sleep, all factors combined, global severity, and global change of the illness; there was no significant difference between dothiepin and amitriptyline in regards to efficacy. However, significant differences in tolerability were

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observed. The amitriptyline group reported the highest frequency of side effects, predominantly dry mouth and drowsiness. Comparison of electrocardiographic effects resulted in significantly less tachycardia and myocardial conduction changes with dothiepin than with amitriptyline (Claghorn, 1984).

The clinical experience abroad (Rees and Marsh, 1975; Rees and Risdall, 1976) has suggested that dothiepin is also effective as an antidepressant at lower doses. Moreover, the drug is frequently prescribed as a single daily night-time dose of 150 mg.

The principal objectives of the present study were to evaluate antidepressant activity, safety, and tolerability of dothiepin in outpatients with major depression, when administered in single daily 150 mg bedtime doses relative to placebo and to an active reference, doxepin 150 mg, at bedtime. As a secondary objective, the question was asked whether computer analyzed EEG (CEEG) brain mapping, after a single Test-Dose, can predict the therapeutic response of patients after 9 weeks treatment. As a final question, the CNS responses of treatment responder and nonresponder patients to antidepressants were investigated.

Materials and Methods

This study was a part of a large multicenter program. Sixty-two (62) patients with the diagnosis of Major Depressive Episode (DSM-III-R 296.2, 296.3), without psychotic features, were screened in this program. Thirty-seven subjects fit the eligibility criteria and the age range of 18 to 74 years (mean age: 36.6 yr.).

A variety of scales were applied to evaluate the effectiveness of the treatment. These included the Hamilton Depression Scale (HAM-D), Clinical Global Impression (CGI), Hamilton Anxiety Scale (HAM-A), and the Montgomery and Asberg Depression Scale.

After a 4- to 14-day washout period (placebo run-in), patients were randomly assigned to 3-day treatment at bedtime with placebo or dothiepin 50 mg or doxepin 50 mg. That was followed by four days of treatment at bedtime with placebo, dothiepin 100 mg, or doxepin 100 mg. At weeks 2–8 dothiepin and doxepin were administered at 150 mg doses. At week 9, a period of deescalation with the dosage reduced by no more than 1 capsule daily was executed. Patients were randomized into the following groups: group 1 received dothiepin, group 2 received doxepin, group 3 received placebo.

In all selected patients, extensive demographic data: medical, psychiatric, family, and drug histories were collected. Physical examinations and laboratory tests were conducted at screening and at the end of treatment. Laboratory evaluations included hematology, blood chemistries, and urine analysis. A urine drug screen and pregnancy test were done at screening only.

EEG Data Collection

Prior to entry into the study, a clinical/diagnostic EEG with Brain Mapping was performed. Subsequently, before, and 1 and 3 hours after the first dose (placebo or dothiepin or doxepin) as well as 1 week, 5 weeks, and 9 weeks (termination) of the treatment, CEEG and Brain Mapping examinations were conducted. EEG was recorded according to the International 10/20 System.

QPEEG Analysis

To determine the Test-Dose response of patients and to establish the central effects of drugs, the quantitative pharmaco-EEG (QPEEG) method (Itil, 1974) was used. For this purpose, EEG data, collected from O_2-A_1 areas of the brain, were analyzed using period analysis.

For each time period (pre, 1, and 3 hours after Test-Dose and after treatment at weeks 1, 5, and 9), and for each type of recording (Resting Recording = R.R., and reaction time recording = R.T.), the mean and standard deviation of the 22 CEEG variables were computed.

Dynamic Brain Mapping

For Dynamic Brain Mapping, all recorded leads were analyzed according to modified zero cross-analysis (HZI's clinical analysis) (Itil, Itil, Eralp, Akman, and Manco, 1988). Twenty-two CEEG measurements of this analysis included 20 frequency bands, average absolute amplitude, and average frequency.

With Dynamic Brain Mapping, the amount of delta, theta, alpha, beta activities are displayed by color coding and displaying these color codes on an anatomically correct brain image. The data from the quantified EEG are displayed on the brain image in the exact location of where the recording electrodes were placed. The areas between electrode locations are interpolated using HZI's blending algorithm (Itil, Mucci, and Eralp, 1991).

In Dynamic Brain Mapping, the amount of delta, theta, alpha, beta activities, over all patients, for each time period in each drug session are averaged. In this way the delta, theta, alpha, and beta activity for the group, for before (pre) and after drug, and the predrug brain map is subtracted from each postdrug brain map to give a change from predrug

state. Thus, any change in the brain map can be attributed to the quantitative effect of the drug.

To determine the CEEG profile of the patients all 20 frequency bands were used. To obtain CEEG profiles of patients, the mean of 20 EEG variables of all leads were compared with the age-matched normals using t-statistics.

Results

Psychopathological Evaluations

When the patients were evaluated based on clinical global impression (CGI) scale, it was observed that the total psychopathology between the groups was not different before the treatment (Table 1).

Each group showed improvement during the treatment. However, improvement was statistically significant only with dothiepin and this was also significantly different from that of placebo.

According to the Hamilton Depression Rating Scale (HAM-D), the mean scores of dothiepin, doxepin, and placebo groups were similar before the treatment (24.9, 23.4, 22.8, respectively) (Table 1). During the course of treatment, each group showed improvement in depressive symptomatology. However, only improvement of active drugs was statistically significant. Compared to placebo only dothiepin showed statistically significant different improvement.

Based on the Montgomery Asberg Depression Scale again each group showed improvement during the study period. However, only dothiepin-induced improvement was statistically significant. Also, the therapeutic effects of dothiepin could be differentiated from placebo.

The anxiety state of patients, evaluated based on the Hamilton Anxiety Rating Scale, was not statistically influenced by any of the drugs.

Considering the small sample size of each group, statistical results of clinical data should be considered cautiously.

Side Effects

There were 17 dropouts in the study. Seven patients were discontinued due to adverse effects: doxepin, 5 patients; dothiepin, 1 patient; and placebo, 1 patient. In conclusion, the number of patients discontinuing treatment because of side effects was higher in the doxepin group than with the dothiepin or placebo groups.

Adverse events were elicited at each visit. Dry mouth (throat) and drowsiness (tiredness) were reported most frequently. Grogginess and sleepiness were reported in all three groups: grogginess, 7 dothiepin patients, 9 doxepin patients, and 2 placebo patients; sleepiness, 7 dothiepin patients, 6 doxepin patients, and 3 placebo patients.

Laboratory Abnormalities

None of the patients were dropped from the program because of abnormal laboratory values, EKG alterations, or EEG findings.

The EKGs performed during the screening procedures were normal or of no clinical significance for all patients. At the end of the treatment period, all EKGs were again without clinical significance. However, EKGs for two patients from the doxepin group reported sinus tachycardia.

Before the start of the study, every patient who was included into the study had a clinical/diagnostic EEG that was normal or borderline clinically insignificant.

Physical examinations conducted before and at the end of the study were within acceptable ranges for all patients.

Vital sign assessments such as blood pressure, pulse rate, and body weight were taken at screening and at every visit. No clinically significant deviations were found in any of the vital signs. There were no statistical procedures performed on vital sign measurements.

CNS Effects of Drugs

CEEG Brain Mapping

In order to evaluate quantitative bioelectrical activity of patients before and during the treatment CEEG and topographic Brain Mapping were conducted.

As far as delta activity is concerned, a slight increase was established in the doxepin group, a lesser degree of increased delta in the dothiepin group (left-posterior temporal area), and none was seen with placebo (Figure 2). Increased delta activity indicates sedative effects, which occur most frequently with doxepin, confirming clinically established drowsiness.

Theta activity, which also suggests sedation but to a lesser degree than delta activity, was also most increased with doxepin. Dothiepin also showed some theta activity in the occipital area, but less than doxepin and more than placebo.

Most beta increase was established with doxepin, a lesser degree with dothiepin, and minimal with placebo. Increased beta activity is seen most with anxiolytic drugs.

HAMILTON DEPRESSION SCALE

	MEANS			STD. DEV.		
STUDY PERIODS	DOTH.	DOX.	PLAC.	DOTH.	DOX.	PLAC.
PRE	24.9	23.4	22.8	4.4	1.7	2.5
WEEK 1	16.8	15.2	17.8	3.2	2.9	4.9
WEEK 2	16.0	13.0	17.8	3.4	2.4	5.0
WEEK 3	16.2	13.7	14.2	5.4	2.8	5.4
WEEK 5	12.4	13.2	14.2	3.1	1.2	4.0
WEEK 7	11.5	12.2	14.4	5.4	2.8	3.7
WEEK 9	11.0	13.7	17.0	8.9	3.5	5.1

P-VALUES*
(THERAPEUTIC EFFECT)
(PRE VS LAST SESSION)

DOTH.	DOX.	PLAC.
0.0003***	0.0004**	0.0103

(SIGNIFICANCE LEVEL P<0.001)

*ACCORDING TO STUDENT PAIRED T TEST, SIGNIFICANT EFFECT OF DOTHIEPIN AND DOXEPIN IS OBSERVED.

P-VALUES **

DOTHIEPIN VS PLACEBO	0.0472*
DOXEPIN VS PLACEBO	0.3515
DOTHIEPIN VS DOXEPIN	0.2700

(SIGNIFICANCE LEVEL P<0.05)

**ACCORDING TO WILCOXON (RANK SUMS) SIGNIFICANT DIFFERENCE BETWEEN DOTHIEPIN AND PLACEBO IS NOTICED.

CLINICAL GLOBAL IMPRESSION SCALE

	MEANS			STD. DEV.		
STUDY PERIODS	DOTH.	DOX.	PLAC.	DOTH.	DOX.	PLAC.
PRE	4.2	4.0	4.1	0.7	0	0.1
WEEK 1	4.0	3.5	2.7	0.4	0.5	0.4
WEEK 2	3.4	3.0	3.5	0.5	0	0.5
WEEK 3	3.8	3.0	3.5	0.4	0	0.5
WEEK 5	3.6	3.0	3.2	0.5	0	0.4
WEEK 7	3.3	3.0	3.3	0.7	0	0.5
WEEK 9	3.0	3.0	3.5	0.7	0	0.7

P-VALUES*
(THERAPEUTIC EFFECT)
(PRE VS LAST SESSION)

DOTH.	DOX.	PLAC.
0.0002***	0.0082	0.0510

(SIGNIFICANCE LEVEL P<0.001)

*ACCORDING TO STUDENT PAIRED T TEST, SIGNIFICANT EFFECT OF DOTHIEPIN IS OBSERVED.

P-VALUES **

DOTHIEPIN VS PLACEBO	0.0414**
DOXEPIN VS PLACEBO	0.5551
DOTHIEPIN VS DOXEPIN	0.0770

(SIGNIFICANCE LEVEL P<0.05)

**ACCORDING TO WILCOXON (RANK SUMS) SIGNIFICANT DIFFERENCE IN DOTHIEPIN VS PLACEBO IS OBSERVED.

MONTGOMERY AND ASBERG DEPRESSION SCALE

	MEANS			STD. DEV.		
STUDY PERIODS	DOTH.	DOX.	PLAC.	DOTH.	DOX.	PLAC.
PRE	27.7	24.7	25.4	6.3	4.0	3.8
WEEK 5	14.8	13.7	19.8	5.9	2.6	4.5
WEEK 9	16.8	15.7	20.5	9.3	3.5	5.5

P-VALUES*
(THERAPEUTIC EFFECT)
(PRE VS LAST SESSION)

DOTH.	DOX.	PLAC.
0.0010**	0.0403	0.0032

(SIGNIFICANCE LEVEL P<0.001)

*ACCORDING TO STUDENT PAIRED T TEST, SIGNIFICANT EFFECT OF DOTHIEPIN IS OBSERVED.

P-VALUES **

DOTHIEPIN VS PLACEBO	0.0220**
DOXEPIN VS PLACEBO	0.7904
DOTHIEPIN VS DOXEPIN	0.0217**

(SIGNIFICANCE LEVEL P<0.05)

**ACCORDING TO WILCOXON (RANK SUMS) SIGNIFICANT DIFFERENCE IN DOTHIEPIN VS. PLACEBO, AND DOTHIEPIN VS DOXEPIN ARE OBSERVED.

HAMILTON ANXIETY SCALE

	MEANS			STD. DEV.		
STUDY PERIODS	DOTH.	DOX.	PLAC.	DOTH.	DOX.	PLAC.
PRE	16.6	17.7	13.4	7.7	5.3	2.9
WEEK 1	13.2	14.0	12.8	4.5	5.8	5.4
WEEK 2	12.5	11.0	10.2	3.4	4.4	2.9
WEEK 3	13.2	12.5	10.5	7.2	6.2	2.9
WEEK 5	11.7	12.0	9.1	5.7	3.4	4.4
WEEK 7						
WEEK 9	11.1	11.5	10.7	4.0	4.2	2.7

P-VALUES*
(THERAPEUTIC EFFECT)
(PRE VS LAST SESSION)

DOTH.	DOX.	PLAC.
0.0039	0.1848	0.0444

(SIGNIFICANCE LEVEL P<0.001)

*ACCORDING TO STUDENT PAIRED T TEST, NO SIGNIFICANT EFFECT OF DOTHIEPIN AND DOXEPIN IS OBSERVED.

P-VALUES **

DOTHIEPIN VS PLACEBO	0.2083
DOXEPIN VS PLACEBO	0.8066
DOTHIEPIN VS DOXEPIN	0.6410

(SIGNIFICANCE LEVEL P<0.05)

**ACCORDING TO WILCOXON (RANK SUMS) NO SIGNIFICANT DIFFERENCE AMONG THE GROUPS IS NOTICED.

TABLE 1. Summary of Statistical Analysis for Each Rating Scale

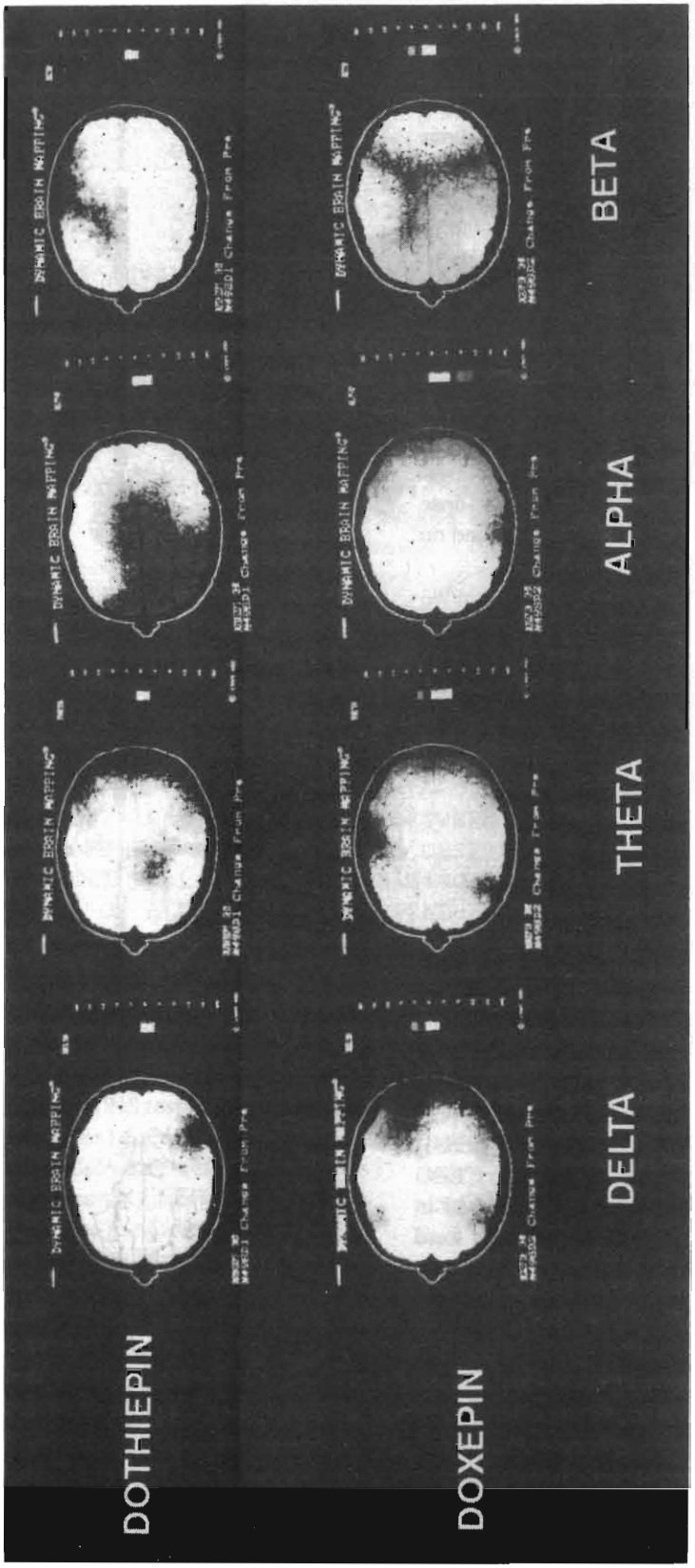

Figure 2. Changes After 3 Hour Drug Administration Based on Dynamic Brain Mapping. This figure shows the changes in EEG frequencies (delta, theta, alpha, and beta) 3 hours after a single oral dose, in comparison to the predrug EEG. The changes of each brain area are shown on a brain map where green to red indicates an increase, and blue to violet indicates a decrease. As can be seen, dothiepin shows an increase of theta activity in posterior areas, and an increase of alpha in frontal leads. In comparison, doxepin shows an increase of delta and theta in the posterior area, a decrease of posterior alpha, and an increase of frontal beta.

Quantitative Pharmaco-EEG

The effects of two active compounds and placebo were investigated using the quantitative Pharmaco-EEG analysis and statistical procedures. The CNS effects of dothiepin were classified in all time periods (after single dose and multiple dose) by the computer data base as most similar to mood elevators/antidepressants, with secondary effects to anxiolytics (Figure 3).

The CNS effects of doxepin were not homogeneous in this group of depressed patients. Antidepressant effects were only established 3 hours after the first dose. One week after chronic administration sedative type CNS effects and 9 weeks after treatment anxiolytic type effects were observed.

The CNS effects of placebo patients were similar to vigilance enhancers during 1 and 3 hours after the first dose (expectancy and increased attention of the subjects), and no significant CNS effects at 9 weeks.

According to ANOVA, based on similarity coefficients, there is a statistically significant difference between groups (p 0.03). Again, according to Duncan's Grouping tests for variables, the biggest difference is seen between the active drug groups (dothiepin and doxepin) and placebo (Table 2).

Behavior-EEG Relationships

Test-Dose Response as Predictor for Outcome

The most interesting findings of this study are the correlations between EEG and clinical findings. As outlined above, each patient in the study received first dose medications (dothiepin or doxepin or placebo as the "Test-Dose") in the EEG laboratory. EEG recordings were done before, 1 and 3 hours after the drug administration. Data were analyzed by the computer according to quantitative Pharmaco-EEG (QPEEG) programs. The changes from predrug to postdrug (or placebo) were evaluated using t-statistics, thus each patient's CEEG response to first dose drug (or placebo) was established in the form of a t-profile. Subsequently, these t-profiles were compared with the well-established drug responses (t-profiles) of antidepressants, anxiolytics, antipsychotics (neuroleptics), and psychostimulants from the data base.

According to Pearson Product Moment Correlation, it was established that 10 of 13 subjects who received dothiepin, 7 of 7 subjects who received doxepin, and only 2 of 10 subjects who received placebo showed positive correlations (similar CNS effects) with antidepressants of the data base (Figure 4).

When we studied the correlations with antidepressants after the first dose (test-dose response) and changes in Hamilton scores (pre vs. 9 weeks after treatment) using linear regression analysis, it was established that there were linear

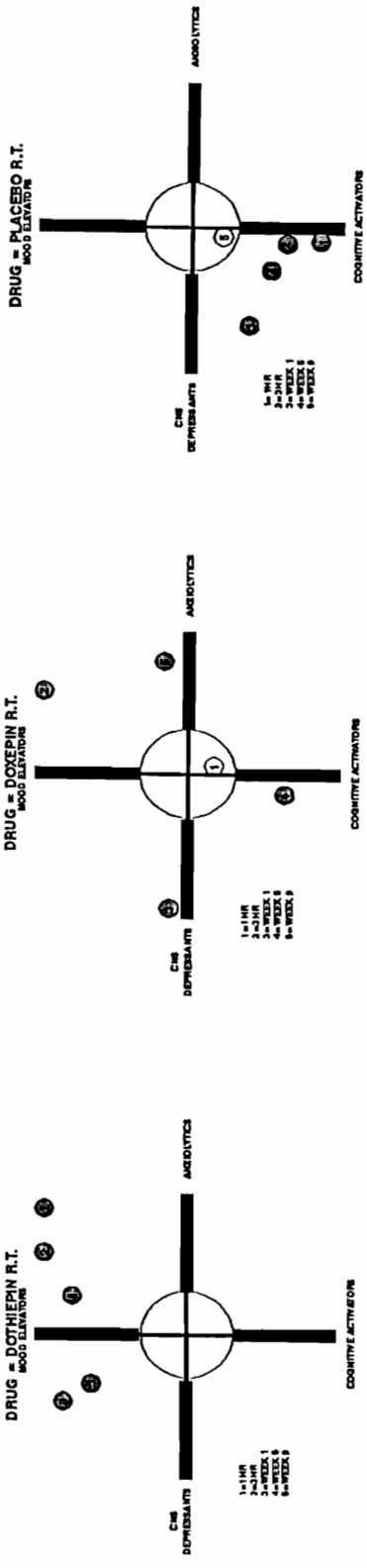

Figure 3. HZI System-I Psychotropic Drug Classification. When the CEEG changes after drug, for the acute dose (1 and 3 hour time periods) and the chronic dose (1-, 5-, and 9-week time periods) were classified against the HZI System-I data base it was observed that the CNS effects of dothiepin, in both the acute and chronic dose classified as similar to Data Base Mood Elevators (Antidepressants, Thymoleptics), whereas doxepin showed similarity to Mood Elevators only 3 hours after single oral dose. The 1-week time period showed similarity to CNS Depressants, the 5-week to Vigilance Enhancers, and the 9-week to Data Base Anxiety Relievers (the 1-hour time period was not classified). Placebo showed similarity to data base Vigilance Enhancers.

DEPENDENT VARIABLE: BASELINE (RT) VS LAST SESSION

Source	Of	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	2.43797922	1.21898941	3.92	0.0324
Error	24	8.07898497	0.31073019		
Corrected Total	26	10.51696419			

R-Square	C.V.	Reset MSE	RTI Mean
0.23184	3904.715	0.557432	0.01427586

Analysis of Variance Procedure
Duncan's Multiple Range Test for variable: RTI
NOTE: This test controls the type 1 comparison error rate, not the experimentwise error rate
Alpha - 0.05 d(- 24 MST- 0.31073
WARNING: Cell sizes are not equal.
Number of Means 2 3
Critical Range 0.544 0.595
Means with the same letter are not significantly different.

Duncan Grouping		Mean		DRUG
	A	0.354	12	DOT
B	A	-0.120	5	DOX
B		-0.249	12	PLA

STATISTICALLY SIGNIFICANT DIFFERENCE BETWEEN ACTIVE DRUG GROUPS (DOTHIEPIN AND DOXEPIN) AND PLACEBO IS OBSERVED. WHEN WE COMPARE THIS RESULT WITH THE CLINICAL SUBJECTIVE RATING SCALES, THIS FINDING INDICATES THE EFFECTIVENESS OF ELECTROPHYSIOLOGICAL PROCEDURES FOR DRUG MONITORING.

TABLE 2. Comparison of the Clinical Changes of the Groups According to the Similarity Coefficients

correlations ($P < 0.05$) between CNS response of individual subjects to the first dose (test-dose) dothiepin, and therapeutic response after 9 weeks multiple dose treatment. Patients who showed the most antidepressant CEEG response to the first dose of dothiepin showed the most improvement after 9 weeks of multiple dose treatment. Although patients treated with doxepin also showed antidepressant response, linear correlation between CEEG response and therapeutic effect did not reach the level of statistical significance. After placebo 8 of 10 subjects showed negative correlation with antidepressants.

EEG Changes After Multiple Dose and Treatment Outcome

CEEG findings between treatment responders (50% or more decrease of Hamilton scores after 9 weeks of treatment in comparison to pretreatment) and treatment nonresponders were also compared. For this purpose, multilead Brain Mapping EEG data based on 20 frequency bands were used. Each group's CEEG pattern was compared with age-matched healthy controls (N = 190).

As seen in Figure 5, therapy responders showed, before treatment, a decrease of slow waves (up to 8.5 cps), and an increase of alpha and beta activities (9.5–26 cps). Decrease in 5.5–6.5 cps and increase in 12.5–15 cps frequency bands reached the level of statistical significance (t-statistics). When this group received 9 weeks antidepressant treatment the CEEG showed marked changes and the EEG difference between the sick group (responder depressed patients) and controls (healthy subjects = zero line) became much smaller than before treatment. The EEG deviations of this

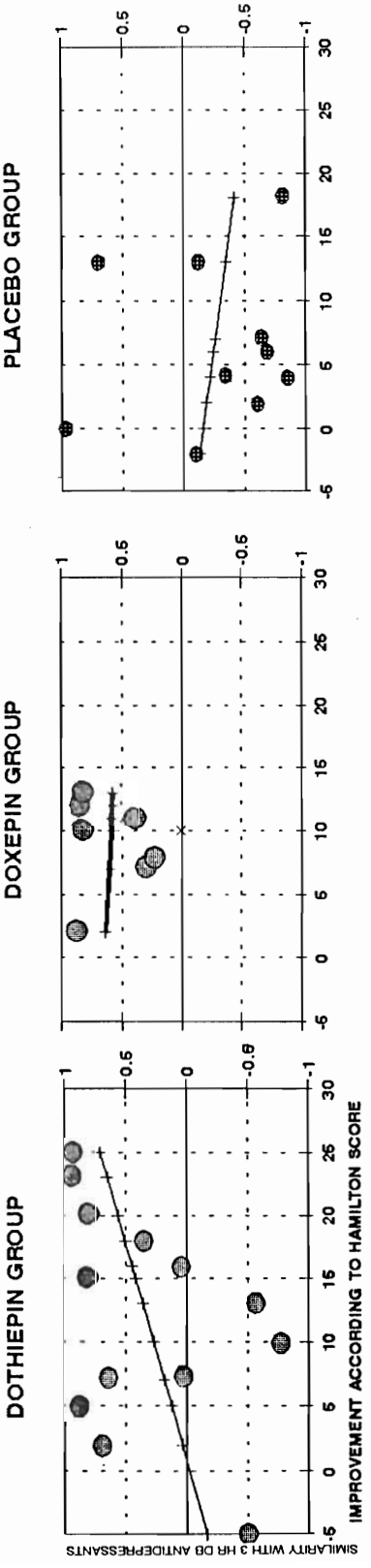

Figure 4. Overall Changes in Hamilton Depression Score vs. HZI 3HR Antidepressant Data Base. The similarity (similarity coefficient of CEEG profiles after first dose of drugs [and placebo] with data base mood elevators [antidepressants]) [y axis] was compared to the overall (mean) improvement of the Hamilton score over the duration of the study (x axis, post- prechanges). As can be seen, the dothiepin group showed a linear correlation between EEG changes after the first dose and improvement of Hamilton scores after 9 weeks treatment. A high similarity of the CEEG profile (pre- postdrug changes) of the Test-Dose antidepressant with the CEEG profiles of the data base antidepressants indicate a high therapeutic response based on Hamilton scores after 9 weeks treatment. The doxepin group did not show a linear trend between EEG and behavior, although the Test-Dose doxepin's CNS effects were also classified as antidepressant. Placebo did not show any consistent trends.

group of depressed patients were almost "normalized" after 9 weeks of treatment with dothiepin.

The CEEG patterns of nonresponder patients before treatment also show a lesser degree of slow waves and more alpha and beta activities than those of healthy subjects, thus similar patterns to treatment responders with minor deviations: Nonresponders have more fast activities above 20 cps and lesser 8.5 and 9.5 cps activities. After 9 weeks of antidepressant treatment the EEG changes in nonresponders in comparison to pretreatment were very slight, certainly much less than those of treatment responder patients (11.5 to 17.0 cps activities further increase and 4.5–5.5 cps activities decrease in nonresponders in comparison to healthy controls). The dramatic difference in EEG changes between responders and nonresponders after antidepressant treatment suggests that patients whose EEG pattern is modified by antidepressant drugs in the direction of "normals" have more chance to show clinical improvement than those whose EEGs do not change or further deviate from the normals. Thus, CEEG seems to reflect the biochemical alterations of the brain. The more "abnormal" biochemistry of the brain of a depressed patient is altered by drug treatment the more the patient has clinical improvement. Thus CEEG may be used as treatment monitoring.

Discussion and Conclusions

This study demonstrated that both dothiepin and doxepin have more therapeutic effect than that of placebo in a group of patients diagnosed as having major depressive disorder. According to both Hamilton and Montgomery Asberg Rating Scales, dothiepin was better discriminated from placebo than doxepin. Statistical significance of the clinical findings have limited value because of the small sample size. As pointed out above, this study was part of a multicenter trial. The results of the analysis of the total study with the patients indicated also that both dothiepin and doxepin are statistically significant with more therapeutic effects than that of placebo. No significant difference was found, however, between the two drugs. Also, in previous studies the therapeutic effect of dothiepin could not be differentiated from amitriptyline. While the therapeutic effect of doxepin could not be discriminated from other tricyclic antidepressants (Lancaster and Gonzalez, 1989), the side effects evaluations provided evidence that dothiepin has less anticholinergic side effects than that of other tricyclics and fewer "stimulant" type side effects of newly developed serotonergic antidepressants (South Wales Antidepressant Drug Trial Group, 1988). A tricyclic with lower clinical and cardiac side effects (Claghorn, 1984), such as dothiepin, has a good chance to be accepted by clinicians.

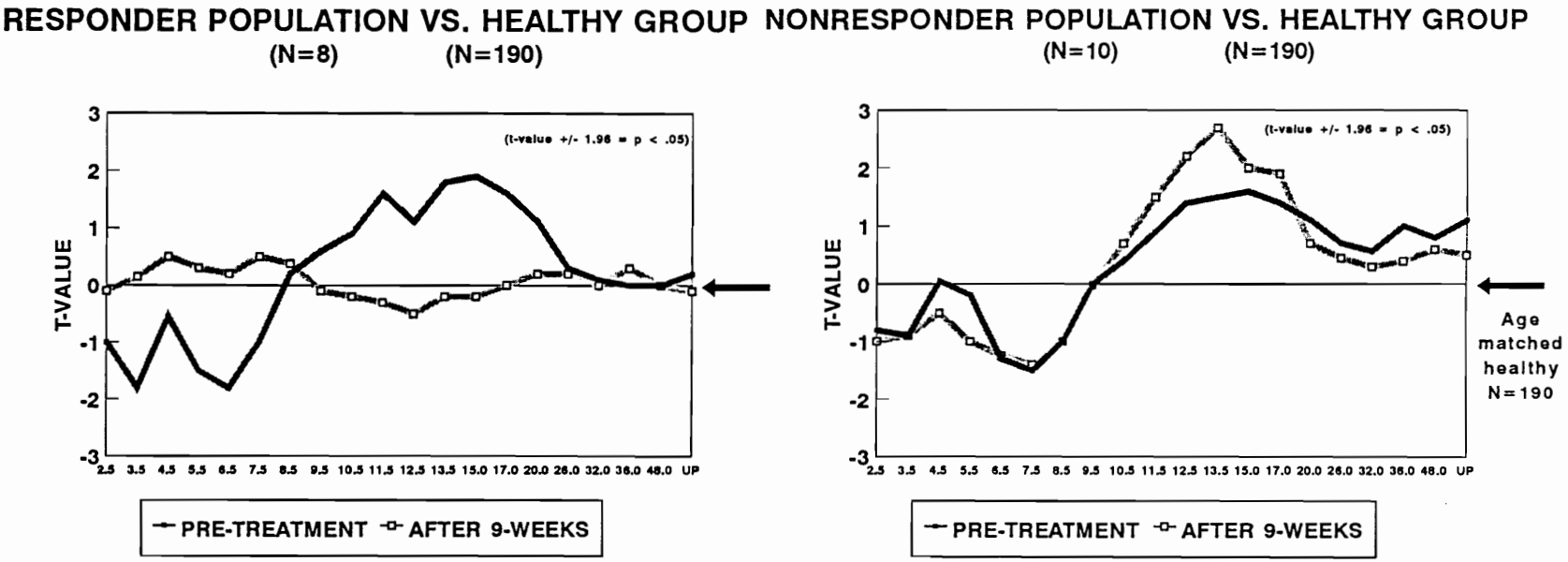

Figure 5. CEEG Profiles of Response of Therapy of Depression Patients to Doxepin or Dothiepin. In this figure the doxepin and dothiepin group patients were separated into responders and nonresponders at the end of the study (based on the Hamilton score). The pre- and posttreatment EEG variables (x axis, based on 20 EEG frequency bands, mean of 14 brain areas), were compared to an age-matched control healthy population's EEG (zero line) using the t-statistic (y-axis). As can be seen, both the responders' and the nonresponders' EEGs show similar CEEG profile to each other before the treatment with less slow activities than the normative group, and more midfrequency activities. After 9 weeks of treatment, the responder group shows large EEG changes (changes toward the normals due to treatment), whereas the nonresponder group does not show any changes from the predrug profile.

This study, although in a relatively small population, sugggests the quantity and the quality of CNS effects after the first dose (test-dose) of an antidepressant, such as dothiepin or doxepin, can be a biological predictor for the outcome. While the clinical antidepressant effects are seen 2 to 4 weeks after treatment with antidepressant drugs the plasma-level studies show that the availability of a substance in blood circulation may be important for therapeutic effects. However, the correlation between plasma levels and therapeutic effects with tricyclic antidepressants in general are inconsistent. This may be explained by the fact that the brain is another "compartment" in a multicompartmental model and the blood-brain barrier may be responsible in the lack of correlation between plasma levels and therapeutic responses in antidepressant drugs. Therefore, a variety of scientists suggested using pharmacodynamic models if the plasma levels of a drug cannot be studied at the "target organ" (U.S. Department of Health, Education and Welfare, FDA, 1977). Since the target organ of antidepressants is the brain, pharmacological effects of antidepressants in the brain should provide reliable information on "bioavailability." Among the variety of methods, quantitative EEG data seem to be suitable to use in pharmacodynamic model (ACNP Final Task Force Report, 1980). Studies have indeed demonstrated that single CEEG measurements can be used for the bioavailability and bioequivalency of psychotropic drugs (Itil and Krynicki, 1983; Itil and Itil, 1986; Itil, Eralp, Mucci, and Siegel, 1990).

Our present study indicates that quantity and quality (type) of CNS effects are important for the therapeutic effects of dothiepin and doxepin. If these antidepressants, after one single test dose, have quantitatively significant and qualitatively predicted (expected) effects on CEEG the drug will also have appreciable therapeutic effects after chronic, multiple dose administration.

The quantitative CEEG changes after a single dose of a drug indicate that the drug and/or its metabolites penetrates through the blood-brain barrier and has effects on the receptors. We would hypothesize that the qualitative effects (predicted changes based on data base classification) suggest that the drug has pharmacological effects in "certain" receptors which may be responsible for the clinical therapeutic effects established after weeks of cumulative administration.

The earlier and more pronounced (after the first dose) the predicted EEG changes (standard EEG response of healthy subjects to antidepressants from the database) occur, and if this new bioelectrical state is sustained during the multiple dose treatment, the more clinical therapeutic effects are expected. The previous studies have demonstrated that all antidepressants increase slow waves and fast activities and decrease alpha waves in quantitative EEG (Itil and Soldatos, 1980). Our recent studies indicate that patients with major depressive disorder have significantly different EEG patterns than those of healthy controls. Antidepressant drug-induced EEG changes (CEEG profile) in our database (Itil, Shapiro, Herrmann, Schulz, and Morgan, 1979) are almost mirror images of EEG profiles of depressed patients (depression EEG versus EEG of age-matched normals).

The CEEG pattern of the depressed patients in this study before treatment was characterized by decreased delta and theta frequencies, and increased alpha and beta frequencies. This pattern was very similar to that of the "depression" CEEG profile of our database. When we separated the total groups into responders and nonresponders after the study, we observed CEEG profiles of both groups before the treatment were relatively similar. Both were significantly different than that of healthy controls. After 9 weeks of treatment (dothiepin or doxepin) the EEG pattern of responders showed marked changes in comparison to pretreatment patterns. They were no more significantly different than those of the healthy controls (EEG was "normalized"). In contrast, the EEG pattern of nonresponders did not show significant change after treatment with antidepressants in comparison to pretreatment. If any change, these were not in the direction of normals but in the opposite direction. These findings support our previous hypotheses that the behavior changes in schizophrenia have close correlations with CEEG changes (Itil, Shapiro, Schneider, and Francis, 1981). Schizophrenics have different EEG patterns than those of controls (more fast activities and more delta waves) (Itil, Saletu, and Davis, 1972). (Neuroleptic drugs decrease fast activities and increase theta and decrease alpha activities) (Itil, 1982). Thus, CEEG profiles of schizophrenia and antipsychotic drugs are almost mirror images (Itil et al., 1981). Just recently we established that CEEG profiles of patients with dementia and the drugs which are claimed to be effective in dementia ("nootropics" or cognitive activators, such as tetrahydroaminoacrin [THA]) are also almost mirror images (Itil, Slone, and Itil, 1990).

Based on the findings of this study one can postulate that different CEEG patterns of depressed patients from normals may reflect the well-hypothesized differences in central biochemistry between two populations. CEEG may be used whether the biochemical "abnormalities" in depression are being reversed (normalized) with an antidepressant drug treatment, thus predicting therapeutic outcome. To test this kind of hypothesis and to establish the value of quantitative EEG in psychiatry a series of World Health Organization sponsored multicenter, multicountry clinical-EEG projects are being developed.

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