A QEEG Database Method for Predicting Pharmacotherapeutic Outcome in Refractory Major Depressive Disorders

Stephen C. Suffin, M.D.
W. Hamlin Emory, M.D.
Nicholas Gutierrez, M.D.
Gurdev S. Arora, M.D.
Mark J. Schiller, M.D.
Arthur Kling, M.D.

ABSTRACT

This prospective, randomized, blinded, controlled study compared outcomes in chronic, refractory major depressive disorder (MDD) with and without physicians' prescribing medications guided by electroencephalography-based medication outcome prediction. There were statistically significant differences between the two groups in pretreatment vs. treatment Hamilton Depression Scale and Beck Depression Inventory scores ($P < .009$) and Clinical Global Impression (CGI) scores ($P = .02$). Only one of six patients demonstrated clinical improvement with medication choice unguided by EEG data, compared to six of seven patients treated with EEG guidance. Pretreatment EEG data predicted medication response in this pilot study.

Introduction

The heterogeneity of medication response within DSM-IV diagnostic classes[1] indicates diverse neurophysiology within disorders.[2,3] Without the ability to distinguish neurophysiologic abnormality, clinicians lack a physiologic basis to guide pharmacotherapy. Selection of neuroactive medication by physiologic criteria is likely to improve therapeutic outcome.[4]

Psychiatric researchers have reported diverse findings with both analog and, more recently, digitized or quantitative electroencephalography (QEEG). Their efforts have generally used behavior as the independent variable and medicated EEG findings as the dependent variable. This approach has not produced clinically useful results. Another approach employs EEG data as the independent variable and medication response as the dependent variable. This demands that patients have a medication-free status similar to that of the asymptomatic controls.

There are reports of medication-free, vigilant, eyes-closed EEG findings in a variety of psychiatric disorders.[5-14] These have demonstrated varied EEG profiles within diagnoses, consistent with a presumption of neurophysiologic heterogeneity. A growing literature designates medication-free baseline EEG data as the independent variable and predicts medication response as the dependent variable, which demonstrates a clear relationship between neurophysiologic findings and treatment response. Patients with obsessive-compulsive and major depressive disorders (MDD) with excess alpha activity are antidepressant responsive,[5,6,8,15,16] though patients with obsessive-compulsive disorder and excess theta activity are antidepressant nonresponsive.[8,16] Patients with hyperactivity disorder and excess slowing are methylphenidate responsive.[11,17] Patients with hypercoherent alpha activity or very low voltage respond poorly to antidepressants and antipsychotics.[18]

We reported a retrospective study of univariate QEEG findings of 100 patients with attentional and mood disorders.[19] Each disorder contained patients with different QEEG features, which robustly correlated with medication class response. Certain clusters of QEEG features required combination pharmacotherapy for optimal clinical response, as if each feature was linearly independent. We subsequently formalized a system of correlating QEEG features with medication response utilizing a database of medication treatment outcomes and refer to this system as referenced-EEG (rEEG).

To test the clinical efficacy of this model, we undertook a prospective, randomized, multiply blinded, controlled pilot study. We sought: (1) to determine whether pretreatment rEEG data predicts the medication response of patients with major depressive disorder (MDD), and (2) to compare the outcomes of MDD patients treated under the current paradigm of physicians selecting medications based upon behavioral markers vs. behavioral markers augmented by rEEG medication correlation.

Methods

Subjects

Two senior faculty members selected subjects from the outpatient clinics at the Veterans Administration Medical Center, Sepulveda, who met operational criteria for chronic MDD and had been nonresponsive to at least two previous medication regimens of adequate dosage(s) and duration—a commonly accepted definition of treatment-resistant depression.[20] The Human Subjects Committee approved this protocol. All study participants provided informed consent after the study procedures had been fully disclosed. Figure 1 outlines the sample selection process.

Concurrent illness was screened by physical examination, hemogram, chemistry panel, thyroid stimulating hormone, urine drug screen, ß-human chorionic gonadotropin (ß-hCG) in female patients, and electrocardiogram. Treating physicians then interviewed patients and provided Hamilton Depression Scale (HAM-D) and Beck Depression Inventory (BDI) scores. Table 1 provides subject characteristics including pre-treatment HAM-D and BDI scores providing an indication of the severity of illness in the study sample. All but two patients (one in each experimental group) had pretreatment HAM-D scores indicating moderate (18-25) to severe depression (>25) and BDI scores indicating moderate to severe depression (19-29) or severe depression (>30).

We excluded patients taking medications other than antihypertensives or hormone-replacement agents. Subjects with a past history of or a current diagnosis of a primary psychotic disorder, intramuscular neuroleptic treatment, documented closed head injury with loss of consciousness, craniotomy, cerebrovascular accident, seizure disorder, dementia, mental retardation, or active substance abuse were also ineligible. All patients were medication free (seven half-lives) and illicit substance free (confirmed by urine drug screens upon EEG testing).

We alternately assigned consecutive patients to control (DSM) and experimental (rEEG) treatment groups. Patients were blind to group assignment. The DSM group received treatment based solely on the joint decision of their psychiatric resident and a supervising faculty psychopharmacologist. Psychiatric residents and

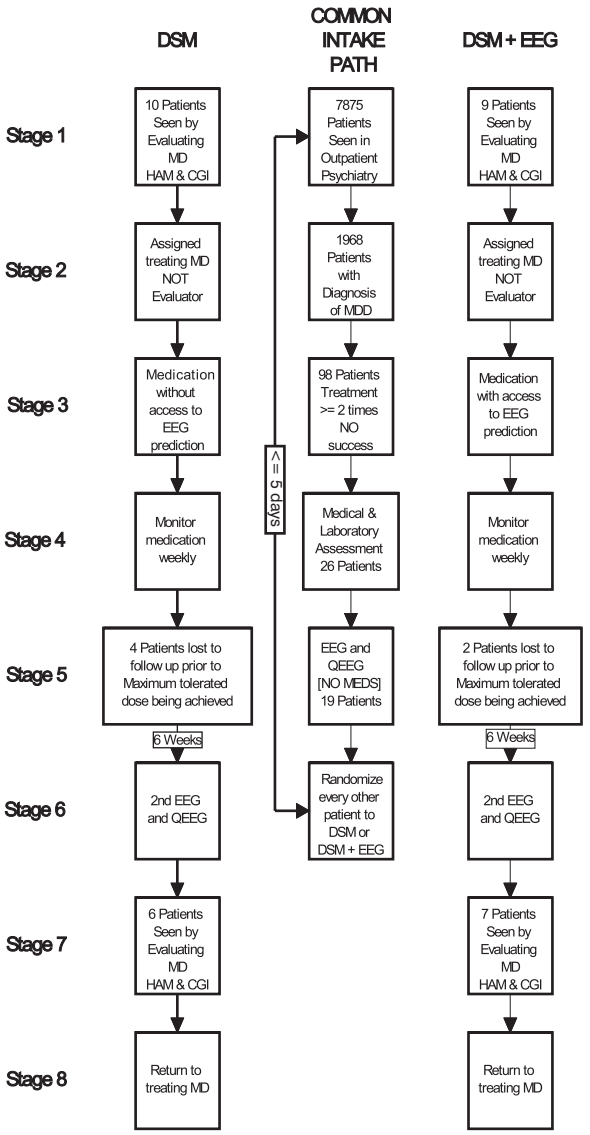

Figure 1. EEG Medication Prediction Pathway

supervising faculty psychopharmacologists treated rEEG patients based on rEEG profile. An experienced, non-treating, blinded clinician provided all clinical ratings. Outcome variables were based on clinical ratings and not on post-treatment EEG changes.

EEG Data Acquisition and Analysis Procedure

All patients received a conventional, eyes closed, awake, digital EEG with linked ear reference according to the International 10/20 System (Spectrum 32, Cadwell Laboratories, Kennewick, Wash.). An experienced EEG technician, blinded to treatment group and medication history, selected at least 32 artifact-free epochs of 2.5 seconds. This sample was fast Fourier transformed into standard EEG frequency bands. The signal features obtained for each electrode site (monopolar derivations) or across electrode pairs (bipolar derivations) included absolute and relative power, asymmetry, mean frequency, and coherence. We log transformed these data to obtain Gaussianity, then age-regressed and z-transformed the results relative to population norms as previously described.[19]

Classification of rEEG Medication Response

We derived rEEG medication response predictions by comparing study patient data to a database of 1,625 medication-free patients containing QEEG findings and subsequent medication outcomes and applied a rule-based classifier using the current

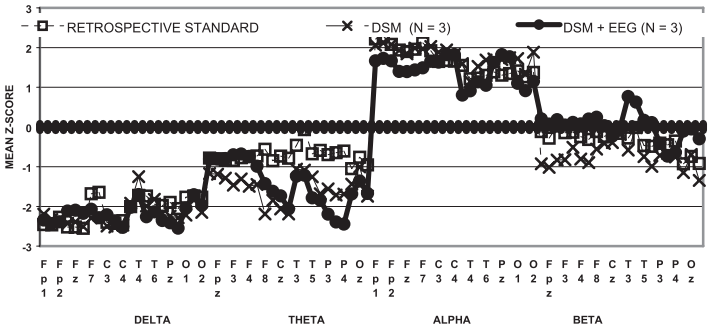

Figure 2. Antidepressant-responsive Spectra

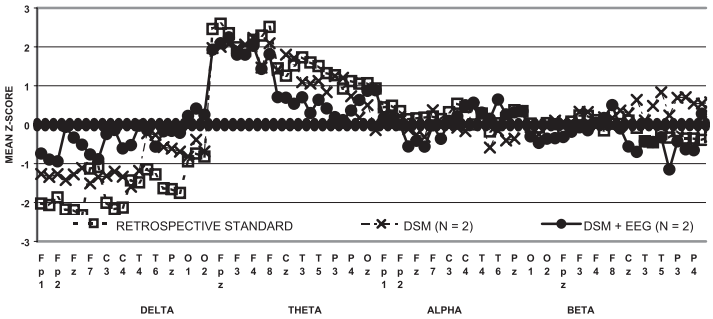

Figure 3. Stimulant-responsive Spectra

patient's data and the database to review pretreatment EEG data. Only the physicians treating the rEEG group and the patient control officer had access to the rEEG outcome predictions.

We incorporated antidepressant, stimulant, and anticonvulsant/lithium responsive spectra identified in previous studies in the rule-based classifier used to predict medication responsivity, which could include medication combinations.[19]

Figure 2 demonstrates the average relative power spectrum of 60 patients with affective and attentional disorders that were antidepressant responsive. This spectrum demonstrates global delta frequency deficit extending posteriorly, a diffuse theta deficit trend with temporal sparing, an alpha maximum in the frontal polar region and a second alpha maximum in the posterior frontal region. These maxima are accompanied by a relative alpha minimum in the temporal region and sustained posterior alpha excess.

Figure 3 demonstrates the average relative power spectrum of 21 patients with affective and attentional disorders that were stimulant responsive. This spectrum exhibits a frontal polar delta frequency deficit. There are two frontal maxima in the theta band. The theta frequency shows temporal excess, gradually diminishing posteriorly. The alpha and beta bands of this spectrum are distributed about a mean Z-score of zero.

Figure 4 demonstrates the average interhemispheric coherence spectrum of 26 patients with affective and attentional disorders that were anticonvulsant and or lithium responsive. This spectrum exhibits posterior delta hypocoherence, posterior theta hypocoherence, frontal alpha hypercoherence, and frontal beta hypercoherence. Our rule-based classifier excluded antidepressant monotherapy in cases of average frontal power less than 9 μV^2 as supported by the literature and our retrospective and unblinded prospective research.[18]

Clinical Monitoring

Treating physicians monitored all patients in weekly sessions. The independent evaluating physician, who had assessed each patient prior to the study start, also assessed each patient after six weeks on maximal tolerated medication(s) dosage (mean follow-up

Table 1. Patient Characteristics, Medication Predictions, and Outcomes

PATIENT NUMBER	GENDER / AGE	TREATMENT GROUP	EEG FINDINGS	MEDICATION RESPONSE PREDICTION 1	MEDICATION RESPONSE PREDICTION 2	MEDICATION RESPONSE PREDICTION 3	MEDICATION SELECTION 1, DOSE IN MG	MEDICATION SELECTION 2, DOSE IN MG	MEDICATION SELECTION 3, DOSE IN MG	PRE-TREATMENT HAMILTON D	END OF TREATMENT HAMILTON D	PRE-TREATMENT BECK	END OF TREATMENT BECK	BLOOD LEVEL OF MEDICATIONS	MEDICATION SELECTION AGREES WITH PREDICTION	END OF STUDY CGI OF EVALUATING PHYSICIAN
1	F / 39	DSM		stimulant	antidepressant		fluoxetine, 40			40	30	30	40		no	0
2	F / 39	DSM		antidepressant			lithium, 600	sertraline, 100		25	20	14	10	?	no	1
3	M / 42	DSM		stimulant	anticonvulsant / lithium		sertraline, 100			20	15	22	18		no	1
4	M / 54	DSM		antidepressant	anticonvulsant / lithium		valproate, 375	clonazepam, 1	lithium, 1800	25	24	23	22	Li = 0.8 meq/ml	no	0
5	M / 51	DSM	low power	no antidepressant monotherapy	no antipsychotic monothereapy		bupropion, 300	lithium, 1200	nefazodone, 300	18	2	23	7	Li = 0.8 meq/ml	yes	3
6	M / 47	DSM		antidepressant	anticonvulsant / lithium	stimulant	fluoxetine, 40			14	19	21	21		no	1
AVERAGE	45									24	18	22	20			
1	F / 38	DSM+EEG		antidepressant	anticonvulsant / lithium		paroxetine, 30	lithium, 600		23	6	27	8	Li = 0.3 meq/ml	yes	3
2	F / 32	DSM+EEG		antidepressant	anticonvulsant / lithium		fluoxetine, 40	valproate, 500		37	X	41	X	valproate = 62 μg/ml	yes	3
3	M / 31	DSM+EEG		antidepressant	anticonvulsant / lithium		sertraline, 100	lithium, 600		22	4	34	6	Li = 0.2 meq/ml	yes	2
4	M / 45	DSM+EEG		anticonvulsant / lithium			valproate, 500			26	14	21	17	valproate = 78 μg/ml	yes	2
5	M / 48	DSM+EEG		stimulant	anticonvulsant / lithium		methyl-phenidate, 30	carbamazepine, 900		22	22	25	26	carbamazepine = 5 μg/ml	yes	0
6	M / 64	DSM+EEG		stimulant			Methyl-phenidate, 25			29	4	30	10		yes	3
7	M / 33	DSM+EEG	low power	no antidepressant monotherapy	no antipsychotic monotherapy		carbama-zepine, 800	fluoxetine, 30		14	6	17	10	carbamazepine = 6.3 μg/ml	yes	2
AVERAGE	42									25	9	28	13			

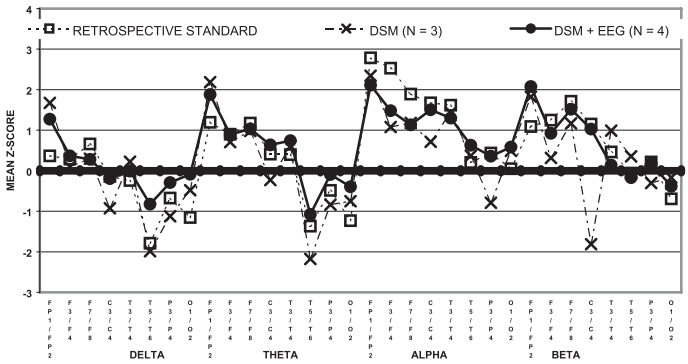

Figure 4. Anticonvulsant/lithium-responsive Spectra

25 weeks). We assigned a Clinical Global Impressions Scale (CGI) (0 = no improvement, 1 = mild improvement, 2 = moderate improvement, and 3 = marked improvement or no residual symptoms with CGI≥2 required to qualify as improved) score.

Results

Neurometric Spectral Features

The average relative power spectra of antidepressant responders, the average relative power spectra of stimulant responders, and the average coherence spectra of anticonvulsant or lithium responders in both treatment groups are shown for comparison (Figures 2, 3, 4). These same figures also illustrate the spectral features recorded in our previous study as indicated above and are quite comparable. One patient in each treatment group had EEG records exhibiting diffusely low power and frontal averages less than 9 μV^2, excluding antidepressant monotherapy.

Main Outcome Measures

Table 1 shows subject characteristics, rating scales, rEEG medication predictions, prescribed medications, and pre- and post-treatment HAM-D, BDI, and CGI values. In addition, Table 1 displays prescribed medications and their final daily dosages for both groups. Tables 2 and 3 show further details on prescribed medications. Medication dosages were within recommended dosage ranges, and plasma levels were obtained for anticonvulsants and lithium. Dosages were within therapeutic ranges for the DSM group but were below threshold for several rEEG patients.

The DSM group HAM-D mean pretreatment and treatment scores were 24 and 18 respectively (25% decline) with BDI mean pretreatment and treatment scores of 22 and 20 (11% decline). The rEEG group HAM-D mean pretreatment and treatment scores were 23 and 9 respectively (60% decline) with BDI mean pretreatment and treatment scores of 26 and 13 (50% decline). The differences in decline between the two treatment groups are highly significant (Friedman ANOVA 2 [N = 13; df = 3], $P<.009$). The rEEG group outcomes (six of seven patients, CGI≥2; three of seven patients, CGI = 3) were significantly better than the DSM group (one of six patients, CGI = 3; five of six patients, CGI = 0 or 1) ($P = .02$, Fisher's Exact).

The rEEG findings predicted that five patients in the DSM group would be nonresponsive to the medications selected, and that the sixth patient in the group who had a low power spectrum would not respond to antidepressant monotherapy. This patient had a favorable clinical outcome (CGI = 3) with combination therapy that included bupropion. Six of seven patients in the rEEG group responded as predicted by EEG data, including one low power spectrum patient who responded favorably (CGI = 2) to combination therapy with fluoxetine and carbamazepine. Combining positive and negative predictions, 11 of 13 response predictions were correct ($P = .015$, Fisher's Exact). These data are associated with an 86% likelihood of positive patient outcome with each prediction, with a Youden Index of 0.8.

Table 2. Medications for DSM Group

Medications	No. of Patients	Mean Dose [mg] in 24 hr
Fluoxetine	2	40
Nefazodone	1	300
Sertraline	2	175
Clonazepam	1	2
Lithium	2	1050
Valproate	2	1125
TOTAL NUMBER OF MEDICATIONS	10	
AVERAGE NUMBER OF MEDICATIONS PER PATIENT	1.7	

Table 3. Medications for rEEG Group

Medications	No. of Patients	Mean Dose [mg] in 24 hr
Fluoxetine	2	35
Paroxetine	1	30
Sertraline	1	100
Methylphenidate	2	27.5
Carbamazepine	2	850
Lithium	2	750
Valproate	2	1000
TOTAL NUMBER OF MEDICATIONS	12	
AVERAGE NUMBER OF MEDICATIONS PER PATIENT	1.7	

Discussion

Patients treated in the DSM group had an inferior response to pharmacotherapy. Only one of six DSM group patients demonstrated improved outcome by HAM-D, BDI, and CGI ratings compared to six of seven rEEG group patients. Furthermore, three of seven patients in the rEEG group achieved remission (CGI = 3), an unanticipated outcome in this chronic, refractory population.

rEEG accurately predicted responsiveness to medications not generally used as frontline treatments for MDD. Some rEEG patients, guided by EEG findings, received initial stimulants in monotherapy and polytherapy. No DSM group patients received stimulants, which are generally used in depression treatment only after multiple antidepressants or antidepressant combinations have failed. Inclusive of stimulant use, however, the average number of agents per patient (DSM = 1.7 and rEEG = 1.8) was the same in both groups and does not appear to explain the differential outcomes. Since initial sequential monotherapy is the most widespread pharmacotherapeutic approach to affective illness,[4,22-24] with augmentative strategies a secondary approach,[25-28] physicians may have treated DSM patients, already deemed refractory, with novel medication selections and frequent polypharmacy.

A primary assumption behind rEEG medication guidance is that patients within DSM diagnostic categories are physiologically heterogeneous. Some patients with a diagnosis of MDD may not favorably respond to antidepressants, because such agents may not improve the neurophysiology represented by certain electrophysiologic abnormalities. One of six DSM and three of seven rEEG patients did not appear to require antidepressants according to rEEG predictions.

The DSM patients who did not improve did not receive an effective combination of non-antidepressants (or antidepressant monotherapy in one case) that were correlated with their rEEG findings. These patients' electroencephalographically demonstrated abnormalities were not accurately addressed, despite the frequent use of augmenting agents in these refractory patients.

This study showed that medication efficacy varied with pathophysiologic types as represented by specific neurophysiologic abnormalities; furthermore, the study indicates that the DSM diagnosis of MDD contains heterogeneous neurophysiology that can be marked by QEEG data. When prospective QEEG data are compared and matched with similar QEEGs and their medication outcomes in a database, physicians can use these referenced EEG data to link medication selection with particular neurobiology, and improve therapeutic efficacy.

This study employed a naturalistic study design in which clinical decisions were based on the choices of competent psychiatrists in general clinical conditions, rather than following a specific, rigid research treatment protocol. This was true even for the experimental group in which EEG guidance suggested treatment direction, but not specific medications. The naturalistic study design was chosen as best for this study, given that rEEG is a diagnostic test that suggests a number of likely treatment alternatives rather than a specific treatment as such. In addition, the randomized, controlled study design tends to remove any bias present in the psychiatrists' treatment choices.

There is debate over the definition of treatment-resistant depression. We used the widely accepted criterion of having inadequate response to at least two antidepressant trials of adequate dosage and duration.[20] Given the difficulty of operationalizing this criterion, we allowed the senior psychiatrists involved to make an assessment of past adequacy and duration of prior medication trials in these subjects diagnosed with chronic major depression. Ultimately, however, the fact that the study used a randomized, controlled design makes this issue somewhat academic, as the study design would tend to remove biases regarding the adequacy of past treatment.

There are limitations to this pilot report, most noticeably a small sample size. In addition, this was a multiply blinded study in which subjects and independent raters were blinded to treatment, but in which treating physicians were not, which may have introduced some bias into the study. Blinding of physicians was difficult to arrange, as this was not a trial of a specific agent or treatment, but one that tested a method for psychiatrists to choose from a range of options.

Conclusions

Despite the limitations of this small study, the robust findings are compelling, and argue for a large, prospective pharmacotherapeutic study.

Stephen C. Suffin, M.D., and **W. Hamlin Emory, M.D.,** are assistant clinical professors; **Gurdev S. Arora, M.D.,** is associate clinical professor; and the late **Arthur Kling, M.D.**, was formerly vice-chairman in the Department of Psychiatry, University of California at Los Angeles. **Nicholas Gutierrez, M.D.**, is an attending psychiatrist, Didi Hirsch Mental Health Center, Los Angeles, Calif. **Mark J. Schiller, M.D.**, is associate clinical professor, Department of Psychiatry, University of California San Francisco. Contact: Mark J. Schiller, M.D., 2299 Post Street, Suite 104A, San Francisco, CA 94115. Tel.: (415) 567-4604. E-mail: mark.schiller@ucsf.edu.

Acknowledgements: The authors wish to express our appreciation to the late Harold H. Kelley, Ph.D., professor emeritus of social psychology, University of California at Los Angeles, for his conceptual suggestions and assistance with editing this manuscript.

Funding: None

Potential Conflicts of Interest: Dr. Suffin and Dr. Emory are founders and Dr. Schiller is director of medical affairs for CNS Response, Inc., which provides QEEG analysis technology.

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