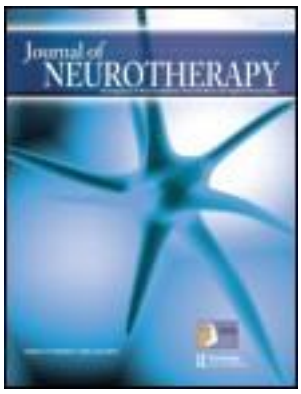

Journal of Neurotherapy: Investigations in Neuromodulation, Neurofeedback and Applied Neuroscience

"First, Do No Harm"- A Basic Tenet in Jeopardy?

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Published online: 07 Sep 2008.

To cite this article: Dr. Daniel A. Hoffman MD (2007) "First, Do No Harm"–A Basic Tenet in Jeopardy?, Journal of Neurotherapy: Investigations in Neuromodulation, Neurofeedback and Applied Neuroscience, 10:4, 53-61, DOI: 10.1300/J184v10n04_06

To link to this article: http://dx.doi.org/10.1300/J184v10n04_06

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"First, Do No Harm"– A Basic Tenet in Jeopardy?

Daniel A. Hoffman, MD

ABSTRACT. This paper reviews recent research with electrophysiology analysis and the ability to predict psychotropic medication response. Four clinical cases are presented which illustrate the harm of inappropriate medication use or medication stacking which is an inadvertent common occurrence. The cases also demonstrate the benefit achieved by using Referenced-EEG (rEEG) to guide medication selection. Instances of unnecessarily or incorrectly medicating patients, as evidenced by both rEEG reports and patient clinical response, are highlighted. The possible inaccuracies of our current DSM nomenclature to describe patient phenotypes, which routinely determine psychotropic treatment, are case illustrated by comparing outcomes achieved using neuroelectrophysiology technology. doi:10.1300/J184v10n04_06

KEYWORDS. EEG, rEEG, QEEG, medication response, biomarker, neuroimaging

INTRODUCTION

Various uses of quantitative EEG are emerging as possible ways to predict positive and adverse psychotropic medication responses (Cook et al., 2002, 2005; Iosifescu et al., 2004; Iosifescu, Greenwald, Devlin, Perlis, et al. 2005; Iosifescu, Greenwald, Devlin, Alpert, et al. 2005; Suffin & Emory, 1995). Recent attention to suicidality associated with antidepressants as well as pos-

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Journal of Neurotherapy, Vol. 10(4) 2006

doi:10.1300/J184v10n04_06

sibly anticonvulsants and stimulants further highlights the usefulness of physiologic predictors, such as EEG biomarkers, when choosing which medications are most appropriate for a patient. In addition, medication stacking, particularly in the treatment-resistant patient, may cause adverse reactions, over-activation or even neurotoxicity. Patients on four to six different drugs present a dilemma best expressed in the quote from the famous advertising guru Oglesby, who stated, "I know half of my marketing dollars are wasted, I just don't know which half." Psychopharmacology is more challenging in that half of the medications may not only be wasted but counterproductive. Intuitively, it is often felt that a patient cannot possibly need so many drugs, but with the fragility of some disorders, it can be difficult and risky to change medications. Equally distressing is the patient who may no longer need any medication but remains on psychotropic drugs for years.

Medication induced changes in EEG and QEEG data have been reported for a broad range of antidepressants, benzodiazepines, stimulants, antipsychotics, lithium salts and anticonvulsants (Itil, Marasa, Bigelow, & Saletu, 1973; Itil, Shapiro, Herrmann, Schulz, & Morgan, 1979; Herrmann, Fichte, Itil, & Kubicki, 1979; Saletu, Anderer, Kinsperger, & Grunberger, 1987; Saletu et al., 1992; Small et al., 1989; Struve, 1987). These drug changes are specific in regard to effects on distinct components of the EEG pattern and are dose dependent, reversible upon medication withdrawal, and measurable across psychiatric syndromes and in asymptomatic volunteers.

A major problem has been the lack of studies comparing the EEGs of medication free patients to the database of medication free, asymptomatic controls. Medication free EEG values are necessary to determine whether drug treatments affected the electrical activity and whether there was a correlation between the drug-induced changes in activity and clinical outcome. Specifically, there are limited medication-free QEEG findings reported in adult major depression, adolescent affective disorders, obsessive-compulsive disorder, schizophrenic disorders and attention deficit hyperactivity disorder (Chabot & Serfontein, 1996; Clarke, Barry, McCarthy, & Selikowitz, 1998; DeFrance, Ginsberg, Rosenberg, & Sharma, 1996; John et al., 1994; Nagase, Okubo, & Toru, 1996; Ohashi, 1994; Prichep et al., 1993; Satterfield, Cantwell, Saul, Lesser, & Podosin, 1973).

For the past two years, I have been using referenced-EEG (rEEG) in over 200 hard-to-treat cases in private practice. rEEG is surfacing as a way to provide psychiatry with a set of clinically useful biomarkers to guide the physician's pharmacotherapeutic choices.

> rEEG builds upon the assumptions that there is significant heterogeneity within any DSM diagnostic category, electrophysiologically and otherwise, and that different electrophysiologic abnormalities are predictably responsive to specific medications in improving electrophysiology and improving clinical outcomes. rEEG is a procedure that compares quantitative EEG (QEEG) data from a medication-free prospective patient to a large database of asymptomatic, medication-free, normal EEG's in order to define an abnormality. (Schiller & Emory, 2005)

With rEEG, the physician receives a report listing the drug classes, subclasses and individual medications ranked in probability of treatment success based on database-recorded patient outcomes associated with the physiologic features of the patient's quantitative EEG. Patients need to be off all medications for at least five half-lives. Seventy-four biomarkers were identified by clinical response determined by Clinical Global Improvement (CGI) scores. These consisted of QEEG variables, which were shown to be of predictive value for drug classes, subclasses and specific medications within the subclasses. For example, whenever certain of these measures were abnormal in a certain way, patients' records also revealed that they did well on that particular medication. Medication rankings are grouped as sensitive (S), intermediate (I) or resistant (R), similar to an antibiotic sensitivity report (Figure 1). This is a statistical probability in which patients with similar electrophysiology responded >80% of the time to an "S" medication, 35-80% for an "I," and < 35% for an "R." Likewise, within a class of drugs, specific medications might be given a rating of 1, 2, or 3, with probability of re-

FIGURE 1. Example of Drug Table in a rEEG Report.

A. Summary of rEEG Type I Findings
The overall level of neurophysiologic abnormality as measured by rEEG features is: **Moderate**

Section 1: Drug Class Correlations		
Drug Class	Sensitivity	Biomarker Predominance
Beta Blockers	**Intermediate**	**Low**
Anticonvulsants	**Sensitive**	**Moderate**
Antidepressants	**Sensitive**	**Moderate**
Stimulants	**Resistive**	**Low**
Correlations are based on a subset of more than 1,600 patients in the rEEG database having (1) similar rEEG features to this patient and (2) a change of two or more improvement in their Clinical Global Improvement Index (CGI).		

Section 2: Individual Medication Responsibility
Subgroup ratings (S, I & R) are based on comparison to other subgroups within the overall medication group. Within the subgroup individual medications ratings (1, 2, 3) are relative to other medications in the subgroup only. When there is only one medication in a subgroup only the subgroup rating appears. Specific medication combinations may be incompatible.

Anticonvulsants (Sensitive)				**Antidepressants (Sensitive)**		
Trade Name	Generic Name	Sensitivity		Trade Name	Generic Name	Sensitivity
Benzodiazepines		S		SSRI		I
Xanax	Aiprazolam	2		Prozac	Fluoxetine	3
Ativan	Lorazepam	1		Zoloft	Sertraline	3
Klonopin	Clonazepam	1		Paxil	Paroxetine	1
Tegretol	Carbamazepine	ND		Luvox	Fluvoxamine	2
Depakote	Divalproex	R		Celexa	Citalopram	2
Neurontin	Gabapentin	S		TCA		R
Lithane	Lithium	S		Norpramin	Desipramine	
Lamictal	Lamotrigine	ND		Tofranil	Imipramine	
Topamax	Topiramate	ND		Pamelor	Nortriptyline	
Beta Blockers (Intermediate)				Elavil	Amitriptyline	
Trade Name	Generic Name	Sensitivity		Anafranil	Clomipramine	
Lopressor	Metoprolol	I		Wellbutrin	Bupropion	S
Inderal	Propranolol	I		Effexor	Venlafaxine	S
Tenormin	Atenolol	I				

sponse being in that ascending numeric order. "ND" refers to the finding where there is not yet enough statistical data in the database for that brainwave signature to make a choice, but the medical director might comment within the report on his experience. Clinical judgment then determines which medication, brand or generic, order, etc., should be implemented. The report is a guide, not a cookbook.

Early research demonstrates that rEEG is effective about three-quarters of the time (Emory, Schiller, & Suffin, 2004; Schiller et al., 2005) in guiding therapy in treatment-resistant patients with a range of psychiatric syndromes, including major depression, bipolar disorder, attention deficit disorder, anxiety, dual diagnosis substance abuse and eating disorders. Previous authors suggest the ability to determine antidepressant medication effectiveness and even suicidality prediction (Cook et al., 2002; 2005; Iosifescu et al., 2004; Iosifescu, Greenwald, Devlin, Perlis, et al. 2005; Iosifescu, Greenwald, Devlin, Alpert, et al. 2005) after taking a medication for several days. Similarly, it is the expectation of the developers of rEEG that future studies may be able to predict a suicide response based on brain function before initiating a medication that could do harm or be ineffective.

Schiller reported on a multi-site case series that examined the use of rEEG in general clinical practice (Schiller et al., 2005). The five clinical sites studied included two general psychiatric practices, a managed behavioral health pilot project, an eating disorder rehabilitation facility, and an addiction medicine practice. Two hundred forty-seven (247) patients were treated following referenced-EEG guidance. In all, 182 (74%) of these treatment refractory patients were rated as either "much improved" or "very much improved." In three sites, a seven-point "Helpfulness Scale" was fashioned after the Clinical Global Improvement scale (CGI) which indicated that rEEG was either "moderately helpful" or "essential" (the top two items on the seven-point scale) in at-

taining the ultimate clinical results in 77% of cases. In a randomized, controlled, multiply blinded VA study (Suffin et al., 2006) of 13 patients with Major Depression having failed at least two prior adequate medication trials, six were treated by DSM direction and seven were medicated with DSM plus rEEG guidance. Six of the seven patients (85%) in the rEEG treatment group demonstrated improvement (yet did not respond to anti-depressants alone) based on pre and post Ham-D's and Beck Depression Inventories. Only one of the seven (15%) in the control group improved (with the improved patient's response being consistent with rEEG predictions).

METHODS

The rEEG report was developed by CNS Response, Inc. using baseline, EEG data from un-medicated patients as well as asymptomatic individuals and predicts which medication will be most effective in alleviating the symptoms of the patient. rEEG standardizes QEEG variables and compares these to a public database of EEG records of non-symptomatic individuals to establish normative values for the rEEG variables.

A proprietary database was collected consisting of >12,000 treatment episodes of >2,000 medication-free psychiatric patients (patients that were at least seven half-lives free of all medications), across a range of DSM disorders, containing EEG and QEEG findings and subsequent medication outcomes. Each case has a record of the patients pre-pharmacotherapy QEEG, the pharmacotherapy prescribed and the patient's symptomatic response over a minimum of 26 weeks and follow-up QEEG data. From this database, statistical analysis was applied to determine a set of multi-variable values of the QEEG that are highly predictive of a patient's response to specific pharmacotherapies. When a patient's QEEG is compared to this database using these multi-variable values an historical response rate of patients with similar QEEG features can be associated with each of the medications in the database and this information added to the clinician's pharmaco-selection process (Schiller & Emory, 2005).

In the original database, each patient had a conventional digital EEG. Twenty-one electrodes were applied according to the International 10 / 20 System. Ten to twenty minutes of eyes-closed, awake, resting EEG was recorded referenced to linked ears. All impedances were less than 5,000 ohms. The EEG amplifiers had a band pass from 0.5 to 70 Hz (3dB roll off per octave). A 60 Hz notch filter was used during the collection process.

The clinician's role today in procuring a report consists of gathering the QEEG in the identical manner in which we do all our neurofeedback assessments. Ten minutes of eyes closed relaxed raw data are then sent to CNS Response to be processed where it is artifacted and conventionally reviewed by a board certified electroencephalographer with certification in quantitative electroencephalography. The data are then submitted to statistical analysis to determine which biomarkers are triggered and how they relate to medication response. Those which have insufficient statistical data, or where there are either too many or too few biomarkers, receive a review by the medical director to make an interpretation–similar to how pap smears are currently processed. A report is then issued back to the clinician, part of which is replicated in Figure 1.

rEEG is typically used to guide medication selection in a treatment-resistant patient. The following cases were selected as examples of recent patients to my practice in which I had no clear clinical direction to follow and where, retrospectively, it was felt the current medication regime was actually harming the patient. The purpose of these cases was to highlight an unexpected outcome when using rEEG (i.e., the inadvertent finding of those who may be harmed by medication). While it is not new to observe that many patients who have been taken off meds for a "wash out" or to "start all over from baseline" have felt better off drugs, the more important questions being asked through this paper is whether this can be objectively determined through evidence found in the QEEG and rEEG.

Cases

Patient 1

A 62-year-old male was previously diagnosed with a long-standing history of Bipolar or

Major Depressive Disorder, Recurrent. He had two previous psychiatric hospitalizations for suicidal ideations and acted on them impulsively, without warning or ability to contract for safety. He also complained of significant fatigue and inability to work and thus was spiraling into a deep depression exasperated by financial problems. His previous psychiatric medication history consisted of: olanzapine, risperidone, venlafaxine, lamotrigine, ziprasidone, lithium, aripiprazole, atomoxetine, zonisamide, ropinirole, buproprion, paroxetine, fluoxetine, sertraline, escitalopram, and methylphenidate. The rEEG report suggested that his best response would be with a combination of oxcarbazepine and nortriptyline, which was implemented and, at last follow up (approximately one-year post rEEG), he related "feeling great," successfully back to work in a new job, outperforming the rest of the office in sales and no longer bothered by fatigue. He also survived the loss of his father from suicide within this time frame without spiraling into another episode. His family found this incredible, considering his history.

Patient 2

A 33-year-old female was accompanied by her husband, both of whom were extremely discouraged about ever being able to lead a normal life due to profound depression and anxiety. She had two hospitalizations that she felt were not beneficial and was close to the point of feeling hopeless. Her 22 previous psychiatric medications were: fluoxetine, paroxetine, citalopram, desipramine, venlafaxine, gabapentin, ziprasidone, olanzapine, lamotrigine, lithium, buproprion, trazodone, divalproex, duloxetine, zolpidem, eszopiclone, buspirone, quetiapine, alprazolam, amitriptyline, modafinil, and mirtazapine. She had a difficult time weaning off the medications for the rEEG testing. Results suggested using an MAOI with possible augmentation with divalproex, carbamazepine or gabapentin. Selegiline was suggested but despite the challenging medication tapering, the patient was feeling so well without medication that, to date, she has decided to only use trazodone for sleep. Her initial Beck's Anxiety score was 58 with a Beck's Depression Inventory II score of 43–both in the severe range. At her last appointment, her scores had normalized to 7 and 1, respectively. As of this writing, she has been medication free for six months, wants to work on her problems in psychotherapy for the first time in her life and is returning to her college education. In the event of needing future medication for her mood, we agreed we would initiate the MAOI.

Patient 3

A 29-year-old female was diagnosed Bipolar I ten years ago, while also in the midst of substance abuse. She was currently on six different medications yet still felt suicidal, labile, sleep deprived and exhausted. Previous medications included: paroxetine, lithium, risperidone, divalproex, venlafaxine, carbamazepine, modafinil, clonazepam, buproprion, and lamotrigine. Upon return for her follow up appointment to review the rEEG results, she stated she felt "wonderful" off medications (the best she had felt in over ten years), slept well and was not tired. Results of the rEEG testing demonstrated a low level of biomarker predominance (the theorized meaning to be discussed below) which has been observed in some patients who feel better without medication. It was decided to remain off medications for now, but if she needed anything, we would implement the rEEG correlations of methylphenidate or dextroamphetamine in combination with divalproex or topiramate. SSRI's would not be used as she showed a resistance to them, but if she needed an antidepressant, she would be more sensitive to the tricyclics. To date (six months post rEEG) she has remained medication free.

Patient 4

A 15-year-old male presented for evaluation of his difficulties in school, learning and behavior at home. He was arrested during an outbreak of explosive behavior, aggression and rage. He was described as having mood swings and was diagnosed previously by both a pediatrician and child psychiatrist as having Oppositional Defiant Disorder and ADHD. He had been on dextroamphetamine for five years. After tapering him off his medications, a QEEG was performed before sending the data for a rEEG report. Since the data appeared normal, I brought

the family back into the clinic to further clarify his symptoms given that the only finding from initial testing was that he was a Right Brained Learner. The rest of the workup was essentially normal. When asking the parents to re-state the problems leading to this evaluation, the mother burst into tears exclaiming there were no current symptoms of aggression, rage, or explosive mood swings now that her son was off the medication. In fact, he was back to being the way he was five years ago, before being diagnosed with Attention Deficit Disorder and treated with psychopharmacology. She was feeling very guilty that she had "created" his problems by making him take the stimulant daily for the last five years. He has remained off all medications for one year, to date.

DISCUSSION

I chose examples of a few cases I see in a busy neuropsychiatric practice where patients routinely have been diagnosed and treated for years, yet significant symptoms remain. In all cases, their initial Clinical Global Severity scores were 6 (severely ill); their Clinical Global Improvement scores were 1 (very much improved); and the rEEG Helpfulness scores, fashioned after the CGI scales, were 1 (essential).

Biomarker predominance is a newly reported measure of the number of biomarkers that are contributing to the sensitivity score in the rEEG. A medication class may be listed as sensitive based on the total score of the contributing biomarkers but that score may be made up of either many markers or comparatively few. If the numbers of markers were few and the class was sensitive then it is likely that those few markers would have individually strong correlation readings. While we do not yet completely know the significance of the report that comes back with low biomarker predominance, it is interesting to note that many of these patients to date feel better without medications (ranging from six to twelve months as of this writing). This is particularly true with a patient population diagnosed and treated in their teen years yet never tried off medications after their mid-twenties when their prefrontal cortex fully developed. Whether some of them will need medications later or not is yet to be determined, but in all cases, if they should, the rEEG suggests that from a physiological perspective, they had not been on the right psychotropics to date and that implementing the correct medications should make a significant difference, as seen by the Schiller multi-site study (Schiller et al., 2005). This has certainly been my experience, with approximately three-fourths of the patients tested resulting in medication changes or combinations that I would have never chosen without the aid of the rEEG. Likewise, this analysis does not imply these patients never needed medication. Their current improvement off psychotropic drugs may not suggest they are necessarily psychologically well, but in all cases the past medications did not lead to clinical improvement, were probably causing psychiatric symptoms and the rEEG report predicted the previous medications would have a low probability of being helpful.

Recent advances in neurophysiology may be signifying that patients' phenotypes and symptom presentations are not accurately reflected in our current nomenclature (Taylor & Vaidya, 2005). Several very depressed patients in whom an antidepressant did not even appear as a correlation on the rEEG report had been on multiple antidepressants for years with no success. The rEEG has suggested such combinations as a beta-blocker or anticonvulsant combined with a stimulant. Anorexics have had medication regimes implicating a stimulant along with a benzodiazepine, something that clinically might appear to be contraindicated but neurofunctionally proved appropriate. Several previously diagnosed ADHD patients with excess frontal beta respond well to gabapentin when taken off their stimulants–as though their brain's idle is set too high and needs to be lowered.

These improved outcomes may be a matter of the subtlety of making the correct diagnosis, inadequacies of current nomenclature or the fact that different brains can clinically present similarly, as suggested by some SPECT scan (Amen & Carmichael, 1997) and QEEG (Prichep et al., 1993) studies. rEEG shows promise not only in helping to accurately determine the correct medications needed for an individual patient, but quite possibly in protecting the patient from an adverse response associated with in-

correct medication selection. Prichep's work, for example, supports this contention by demonstrating that OCD segregated into two different brain signatures: one with an 82% response to medication and the other with an 80% failure rate. Clinically these groups were indistinguishable (Prichep et al., 1993).

There are other reasons to consider rEEG in addition to the patient's symptomatic relief and iatrogenic protection discussed in this paper. Implications for increased remission rates, as well as lower health care costs, also suggest reasons rEEG should be seriously investigated. For example, when informally reviewing cases with colleagues regularly using rEEG guided psychopharmacology, a shorter time span to recovery, along with the need for fewer overall medications, is anecdotally observed. Additionally, the number of medication trials was also felt to be reduced. Increased medication compliance, which leads to lower morbidity and decreased costs, can be as high as 96-98% after twenty-four months. This compares to only one-third these rates when correct drugs are not prescribed (Monastra, 2005). By the efficient use of typically expensive psychotropic medications as well as use of a psychiatrist's time, avoiding unnecessary psychotropic drug stacking, or eliminating medications entirely (as suggested by some of the cases above), cost containment can be realized by both individuals and insurance companies. Prescribing MAOI's and tricyclics, as well as generics in general, significantly increases with rEEG guided therapy. By targeting the medication response with objective evidence, the previously reluctant practitioner might now have the confidence to choose a medication with a higher side effect profile. Having a neurophysiologic basis for that decision increases the comfort level and likelihood of the physician using these medications with less trepidation and increased success. Certainly more controlled research seems warranted to pursue rEEG's place in modern psychiatry.

CONCLUSION

A comment on the relevance of this paper to the neurofeedback community may put this paper in perspective. There are several imperative reasons for neuronal community involvement.

- Any electrophysiologic breakthrough relating to patients should be part of the neurotherapy purview.
- The more we integrate into traditional medical therapies, the more accepted our treatment modalities will become. This offers a direct path, a doorway, in which the success of neurofeedback can also be brought to the attention of prescription writers and mainstream medicine.
- An opportunity presents itself to help be a part of a new era in medication prescribing, if not becoming, in part, a gatekeeper. Members of the International Society for Neuronal Regulation (ISNR) have the electrophysiologic experience and deal with this kind of patient population. This has the potential for being on the front lines of, and contributing to, a potentially significant advancement.
- While most neurofeedback providers do not have prescription writing authority, the need for our knowledge of electrophysiology can begin to blur the lines between the drugs versus no-drugs debate. We can form teams that both ideologies need. Few therapists never feel medications are needed with their patients, if not mandatory to do neurofeedback. Likewise, it offers us exposure to vast numbers of patients who can learn about other non-medication solutions and give them informed choices. In the event we can get patients off medication with improved functioning, a true win/win therapeutic response would have been achieved.
- Lastly, we can help effectively treat patients in trouble while forming collegial relationships in a multi-disciplined environment with those providers who have not had the privilege of understanding all we have to offer their patients.

In conclusion, if it is good for patients, it has to be good for the tenets of ISNR. There are not many of these blended opportunities.

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doi:10.1300/J184v10n04_06