EDITORIAL

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Prediction of Response to Antidepressants: Is Quantitative EEG (QEEG) an Alternative?

Dan V. Iosifescu

Depression Clinical and Research Program, Massachusetts General Hospital, and Harvard Medical School, Boston, MA, USA

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Correspondence
Dan V. Iosifescu, M.D., M.S., Depression Clinical and Research Program, Massachusetts General Hospital, and Harvard Medical School,
50 Staniford Street, Suite 401, Boston, MA 02114, USA.
Tel.: 617-724-7741;
Fax: 617-724-3028;
E-mail: diosifescu@partners.org

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Selecting the most effective antidepressant for depressed subjects having failed previous treatments is difficult; the rates of success are relatively low. There is a clear need for objective biomarkers which could assist and optimize such treatment selection. We review here the current literature and recent developments on the role of quantitative EEG (QEEG) predictors of treatment outcome in major depressive disorder.

Although partial or inadequate response to antidepressant treatment is common in major depressive disorder (MDD), only about 30–40% of the patients who receive adequate pharmacotherapy will achieve full remission (absence or near absence of symptoms) [1]. In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, only 29% of 2876 MDD subjects treated with the maximum tolerated dose of citalopram (up to 60 mg) for up to 14 weeks achieved remission [2]. Nonresponse to antidepressants is associated with disability and higher medical costs [3], and partial response is associated with higher relapse and recurrence rates [4].

The absence of clinical or biological predictors of treatment outcome in MDD is frustrating to both clinicians and patients. The patient's suffering is extended through at least a 4- to 6-week treatment period, and often longer, before nonresponse with that medication can be established. Moreover, the choice of next-step strategies after a failed trial is not clear, especially because some patients do well with a medication even if they failed another medication in the same class. An ideal predictor of treatment outcome would be present in many or all patients and would have high (close to 100%) positive and negative predictive values (i.e., if the predictor is present, all patients with the predictor would have the outcome of interest, and if the predictor is absent, none would have the outcome). To be of clinical utility, the predictor would have to be relatively easy to measure (including cost considerations) and present either at baseline, or before the onset of antidepressant treatment, or early during the treatment (during the first week).

Several clinical variables such as comorbid anxiety disorders [5], substance use disorders [6], and medical illness [7] have been associated with lower rates of improvement with antidepressant treatments. However, clinical variables have proven to be inconsistent predictors, with only limited value in selecting the next-step treatment after an initial failure [8]. Genetic [9] and neuroimaging [10,11] studies have suggested specific correlates of response to antidepressant treatment, but none has yet been prospectively validated. Moreover, the relatively low prevalence of some proposed genetic predictors and the high cost of the imaging tests make such predictors problematic for widespread clinical use.

Electroencephalography (EEG) is an established technique to investigate central nervous system (CNS)

activity. In the search of predictors, EEG has obvious advantages: it is widely available and has a relatively lower cost (compared with neuroimaging). A more modern version is quantitative EEG (QEEG), in which a digitized signal on magnetic or optical media replaces paper tracings, which has enabled computerized spectral analysis of EEG signals, providing information that cannot be extracted through visual inspection of EEG alone.

Studies investigating EEG parameters in relation to clinical outcomes go back several decades, but most of these studies are hard to compare, as they differ in regard to the EEG features examined, the time points of examinations, the EEG electrode montages, and the analytical methods utilized. Moreover, few early studies controlled for potentially confounding variables. However, these earlier reports highlight the potential of QEEG as a potential predictor of outcome to antidepressants. A number of pretreatment EEG parameters were reported to differentiate responders from nonresponders to tricyclic antidepressants (TCAs), especially in the alpha [12] and theta bands [13]. More recently, lateralized baseline alpha power was also associated with response to fluoxetine [14]. The measures of brain response to a stimulus such as the loudness dependence of auditory-evoked potentials (LDAEP; which may reflect the activity in the brain's serotonergic system) have also been associated with response to selective serotonin reuptake inhibitors (SSRIs) [15].

A series of studies at the University of California at Los Angeles have investigated cordance, a QEEG measure integrating absolute and relative powers of the EEG signal [16]. In two small case series, frontal decreases in theta cordance as early as 48 hours after beginning open-label SSRI or serotonin and norepinephrine reuptake inhibitors (SNRI) antidepressants predicted clinical improvement at 8 weeks [17,18]. In a follow-up study including 51 MDD patients treated with fluoxetine or venlafaxine versus placebo, decreases in prefrontal theta cordance at 1 week after the start of medication significantly predicted antidepressant response (measured at week 8 as final 17-item Hamilton Rating Scale for Depression (HamD-17) <10) [19]. Using prefrontal theta cordance "decrease/no decrease" at 1 week as a predictor of clinical response (observed at week 8) led to an accuracy of 72% (sensitivity 69% and specificity 75%). Interestingly, placebo responders exhibited a different pattern of QEEG change (increases in prefrontal cordance at 4 and 8 weeks) [20].

Given that these previous studies indicate mostly prefrontal EEG changes in relation to treatment response, more recently, we used a simple four-channel EEG to investigate prefrontal theta-band relative power as a predictor of treatment outcome. In a cohort of 68 MDD outpatients treated with open-label SSRIs for 8 weeks, frontal theta-band relative powers at baseline and at week 1 were significant predictors of treatment response (defined as HamD-17 reduction $>50\%$ after 8 weeks) [21]. Frontal theta power at week 1 predicted response with a 67% overall accuracy (71% sensitivity and 61% specificity). We retrospectively defined a three-parameter Antidepressant Treatment Response (ATR) index (combining EEG parameters from baseline and week 1). The ATR index improved the predictive ability to 76% accuracy (81% sensitivity and 72% specificity). Recently, preliminary results have been reported from the large multicenter Biomarkers for Rapid Identification of Treatment Effectiveness in Major Depression (BRITE-MD) study. BRITE-MD tested prospectively the predictive ability of the ATR index in 220 MDD patients who started treatment with escitalopram and 1 week later were randomized to continue escitalopram, switch to buproprion, or augment with buproprion [22]. ATR had a 74% accuracy in predicting both response and remission, whereas clinical parameters or genetic polymorphisms were associated with neither response nor remission.

Other studies suggest that baseline QEEG parameters may also serve to predict the total burden of treatment-emergent side effects [23] or, more specifically, to predict treatment-emergent suicidal ideation [24].

In the best-case scenario, QEEG may offer relatively simple and inexpensive predictors of treatment response, with potential additional usefulness in predicting side effects. It is premature to conclude whether QEEG will fulfill its promise, but the data so far support a cautious optimism. The question remains: will such a predictor be useful in clinical practice? Can we trust the early prediction of future nonresponse and switch treatments early, after only 1 week? The BRITE-MD study is only beginning to answer this most important question; more data will be needed to prove the role of QEEG predictors in the process of selecting next-step antidepressant treatments.

Conflict of Interest

Dr. Iosifescu has received research support from Aspect Medical Systems, Forest Laboratories, and Janssen Pharmaceutica. He has been a consultant for Forest Laboratories, Gerson Lehrman Group, and Pfizer, Inc., and a speaker for Cephalon, Inc., Eli Lilly & Co., Forest Laboratories, and Pfizer, Inc.

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