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Comparative effectiveness of biomarkers and clinical indicators for predicting outcomes of SSRI treatment in Major Depressive Disorder: Results of the BRITE-MD study

Andrew F. Leuchter [a,b,*], Ian A. Cook [a,b], Lauren B. Marangell [c], William S. Gilmer [d], Karl S. Burgoyne [b,e], Robert H. Howland [f], Madhukar H. Trivedi [g], Sidney Zisook [h], Rakesh Jain [i], James T. McCracken [b], Maurizio Fava [j], Dan Iosifescu [j], Scott Greenwald [k]

[a] Laboratory of Brain, Behavior, and Pharmacology, Semel Institute for Neuroscience and Human Behavior at UCLA, Los Angeles, CA, United States
[b] Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, Los Angeles, CA, United States
[c] Department of Psychiatry, Baylor College of Medicine, Houston, TX, United States
[d] Department of Psychiatry, Northwestern University, Chicago, IL, United States
[e] Department of Psychiatry, Harbor-UCLA Medical Center, Los Angeles, CA, United States
[f] Western Psychiatric Institute and Clinic, University of Pittsburgh, Pittsburgh, PA, United States
[g] Department of Psychiatry, University of Texas Southwestern Medical School, Dallas, TX, United States
[h] Department of Psychiatry, UCSD, San Diego, CA, United States
[i] Psychiatry, RD Clinical Research, Houston, TX, United States
[j] Department of Psychiatry, Massachusetts General Hospital, Boston, MA, United States
[k] Neuroscience, Aspect Medical Systems, Norwood, MA, United States

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ABSTRACT

Patients with Major Depressive Disorder (MDD) may not respond to antidepressants for 8 weeks or longer. A biomarker that predicted treatment effectiveness after only 1 week could be clinically useful. We examined a frontal quantitative electroencephalographic (QEEG) biomarker, the Antidepressant Treatment Response (ATR) index, as a predictor of response to escitalopram, and compared ATR with other putative predictors. Three hundred seventy-five subjects meeting DSM-IV criteria for MDD had a baseline QEEG study. After 1 week of treatment with escitalopram, 10 mg, a second QEEG was performed, and the ATR was calculated. Subjects then were randomly assigned to continue with escitalopram, 10 mg, or change to alternative treatments. Seventy-three evaluable subjects received escitalopram for a total of 49 days. Response and remission rates were 52.1% and 38.4%, respectively. The ATR predicted both response and remission with 74% accuracy. Neither serum drug levels nor 5HTTLPR and 5HT2a genetic polymorphisms were significant predictors. Responders had larger decreases in Hamilton Depression Rating Scale (Ham-D_{17}) scores at day 7 ($P=0.005$), but remitters did not. Clinician prediction based upon global impression of improvement at day 7 did not predict outcome. Logistic regression showed that the ATR and early Ham-D_{17} changes were additive predictors of response, but the ATR was the only significant predictor of remission. Future studies should replicate these results prior to clinical use.

1. Introduction

Major Depressive Disorder (MDD) is a leading cause of disability with total costs to society in excess of $80 billion annually; approximately two-thirds of these costs reflect the enormous disability associated with MDD (Greenberg et al., 2003; Kessler et al., 2006, 2003, 1994). One reason for these high costs is the length of time it takes for patients to recover. Although controlled efficacy trials suggest that most patients respond to treatment within 8 weeks (Papakostas et al., 2007), the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial found that fewer than 50% of patients responded to the first trial of a serotonin selective reuptake inhibitor (SSRI) antidepressant (citalopram) and fewer than one-third achieved remission (Trivedi et al., 2006). Under standard care, the proportion of patients responding and remitting usually is even lower (Katon et al., 1996, 1999; Trivedi et al., 2004). Consequently, achieving response or remission with an initial medication remains a challenge for most patients with MDD and their physicians.

At present, there is no reliable method for predicting whether a medication will lead to response or remission other than "watchful waiting." Methods to predict which medication would most likely

* Corresponding author. Laboratory of Brain, Behavior, and Pharmacology, Semel Institute for Neuroscience and Human Behavior at UCLA, Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, 760 Westwood Plaza, Rm. 37-452, Los Angeles, CA 90024-1759, United States. Tel.: +1 310 825 0207; fax: +1 310 825 7642.
E-mail address: afl@ucla.edu (A.F. Leuchter).

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benefit an individual patient could reduce patients' suffering. Such tools might include clinical features, biomarkers such as brain-imaging findings, or genetic polymorphisms (Bearden and Freimer, 2006).

Clinical characteristics have the advantage of being relatively easy to determine, but generally have not been useful for predicting response to particular medications. Symptom clusters such as anxiety or melancholia are associated with the overall likelihood of recovery but have not been shown to be reliable predictors of response to a specific medication for an individual patient (Fava et al., 2008; Rush, 2007; Small et al., 1995; Trivedi et al., 2006). Brain imaging also has been shown to have some promise for predicting response to treatment. Data suggest that pretreatment cerebral metabolism, white-matter lesions, or atrophy may be associated with outcome (Konarski et al., 2007), but the burden and cost of these procedures have limited their clinical adoption. Some genetic biomarkers, most notably genetic polymorphisms in the serotonin system, have been shown to influence the outcome of SSRI treatment. Two common and promising candidate polymorphisms are those in the promoter region of the serotonin transporter (5HTTLPR) and in the 5HT2a postsynaptic receptor, which in some studies have been associated with treatment response (Anguelova et al., 2003; McMahon et al., 2006).

One biomarker that has promise as a predictor of treatment response is quantitative electroencephalography (QEEG). QEEG power in the theta and alpha frequency bands (Knott et al., 1996; Ulrich et al., 1994, 1988) may identify patients who are most likely to respond to tricyclic antidepressants (TCAs) or SSRIs. Recent studies found that QEEG changes in the prefrontal region may reliably identify antidepressant medication responders within the first week of treatment (Cook et al., 2002; Leuchter et al., 1999). These findings are consistent with the fact that rhythmic midline prefrontal EEG activity has been shown to reflect the activity of the anterior cingulate and midline prefrontal cortex (Asada et al., 1999), brain areas implicated in mood regulation and the pathogenesis of depression. Refinement of this method might permit use of a limited electrode array in the prefrontal region (Iosifescu et al., 2006; Leuchter et al., 2005; Poland et al., 2006) that would be practical for routine clinical use.

The Biomarkers for Rapid Identification of Treatment Effectiveness in Major Depression (BRITE-MD) study was designed to evaluate several possible biomarkers and clinical measures that might be useful to help direct antidepressant medication decisions. The protocol assessed the predictive value of a frontal QEEG parameter, the Antidepressant Treatment Response (ATR) index (Aspect Medical Systems; Norwood, MA), which incorporates several EEG features determined from previously collected EEG datasets to be associated with response and/or remission during antidepressant treatment (Cook et al., 2002; Iosifescu et al., 2006; Leuchter et al., 2008). In this initial report from BRITE-MD, we tested the primary hypothesis that the ATR at 1 week after initiation of treatment with the SSRI escitalopram would predict response and remission after 7 weeks of treatment. We further tested the hypothesis that early changes in depressive symptom ratings, 5HTTLPR and 5HT2a genetic polymorphisms, and escitalopram serum levels, as well as investigator predictions based upon clinical impression, also would predict treatment response and remission.

2. Methods

2.1. Overview

The BRITE-MD study (ClinicalTrials.gov NCT00289523) was conducted at nine sites (departments of psychiatry at Baylor College of Medicine, Harbor-UCLA Medical Center, Massachusetts General Hospital, Northwestern University, UCLA Westwood, UCSD, University of Pittsburgh, and University of Texas Southwestern, as well as RD Clinical Research, a freestanding research facility). Institutional Review Boards approved the methods of the study.

2.2. Subjects

Three hundred seventy-five subjects, 18–75 years of age, who met the DSM-IV criteria for Major Depressive Disorder, based on the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1997), were enrolled in the study. All subjects had a Quick Inventory of Depressive Symptomatology-Self Rated version (QIDS-SR16) (Rush et al., 2003) score ≥ 12, were in good physical health (i.e., free of any medical condition sufficiently serious to affect brain function), and had no history of seizures, brain surgery, skull fracture, significant head trauma, or previous abnormal EEG. All subjects gave informed consent prior to assessment or any study procedures.

Subjects were excluded from the study if they could not give informed consent, were pregnant or refused to use medically acceptable birth control during the study, met criteria for bipolar or psychotic disorder or substance dependence or abuse within the past 6 months, suffered from cognitive disorder, or met criteria for Axis II cluster A or B diagnosis sufficiently severe to interfere with completion of the protocol. Subjects also were excluded if they had failed to benefit from an adequate trial of treatment or failed to tolerate either of the study medications during the current episode, had a course of ECT within the past 6 months, had a contraindication for use of either of the study drugs, had been treated with fluoxetine or a monoamine oxidase inhibitor (MAOI) within the past 4 weeks, were clinically stable on current antidepressant medication(s) or had started specific psychotherapy for depression (i.e., CBT, IPT) within the past 2 months. Subjects were tested and excluded for use of illicit substances or certain other central nervous system active medications within 1 week prior to enrollment, including antidepressants, anticonvulsants/mood stabilizers, anticholinergics, antipsychotics, migraine medications, Parkinsonism medications, barbiturates, benzodiazepines, herbal preparations, muscle relaxants, psychostimulants, and systemic corticosteroids. Medications acceptable for occasional use (not within 48 h of a QEEG) included non-sedating antihistamines, codeine- or oxycodone-containing compounds, over-the-counter cold remedies, cough suppressants, and non-prescription sleep aids. After complete description of the study to the subjects, written informed consent was obtained.

2.3. Treatment

Study medications were administered in an open-label manner. Subjects received escitalopram, 10 mg daily, for 1 week, after which time they were randomized either to continue escitalopram, 10 mg (ESC; primary study arm), switch to bupropion XL, 300 mg (BUP), or combine escitalopram, 10 mg, with bupropion XL, 300 mg (COMB). For this initial report, we present only the results for the ESC group through the primary endpoint because this was the group that received continuous treatment with a single agent throughout the trial, and for which the clinical symptom changes in the first week of treatment would be most interpretable. Treatment continued at this dosage through 7 weeks (day 49) (1 week of initial treatment with escitalopram plus 6 weeks after randomization), the primary study endpoint (Fig. 1). If reduction in dose was clinically indicated, the subject was removed from the study.

If the subject achieved remission at the primary endpoint, the escitalopram was continued at the same dosage, but if the 17-item Hamilton Depression Rating Scale (Ham-D_{17}) score remained >7, escitalopram could be increased to 20 mg qd no later than day 53 and dosage continued as tolerated through 91 days of treatment (total 13 weeks). At the end of week 13, the Ham-D_{17} and IDS scores were assessed.

2.4. Assessment

All subjects underwent diagnostic assessment with the MINI. Subjects over 60 also were assessed with the Mini Mental State Examination (MMSE) (Folstein et al., 1975) and those with an MMSE ≤ 24 were evaluated by a study physician using a DSM-IV checklist for dementia. Eligibility for the study also was determined using the QIDS-SR_{16} as described above.

The primary efficacy measure was the Ham-D_{17} (Hamilton, 1960) assessed at 7 weeks (day 49). Response was defined as a decrease in the Ham-D_{17} ≥ 50% from the baseline value and remission as a Ham-D_{17} ≤ 7. Severity of depression at baseline also was assessed using the Inventory of Depressive Symptomatology-Clinician-rated (IDS-C_{30}) (Rush et al., 1996) and the Ham-D_{17} to measure core diagnostic and commonly associated symptoms of depression. The IDS-C and Ham-D_{17} were administered using a combined structured interview guide (www.ids-qids.org). Severity of illness also was assessed using the Clinical Global Impression Scale (CGI) (Guy, 1976), and at day 7 a study physician used a modified CGI to make a clinical prediction of the likely degree of benefit that each subject would obtain from 6 weeks of escitalopram treatment: 0 = no significant predicted benefit, 1 = predicted improvement but not response, 2 = predicted response but not remission, and 3 = predicted remission.

2.5. EEG biomarker methods

EEG data were collected using Aspect Medical Systems' NS-5000 system. This consisted of a PC-compatible laptop computer connected to a four-channel EEG acquisition device (BIS×4) that performed digitization as well as signal filtering and conditioning, connected through a shielded cable to six self-prepping electrodes (Zipprep™) (Aspect Medical Systems; Norwood, MA) applied at four recording sites on the forehead (Fpz, FT7, FT8, ground) and two on the earlobes (A1, A2) (Fig. 2). EEG data were recorded while the subject rested in a reclining chair during two 6-min eyes-closed segments, separated by a 2-min eyes-open segment.

Following rejection of artifact, power spectra of the EEG (A1-Fpz, A2-Fpz) were calculated using 2-s epochs of an eyes-closed resting period. Values were calculated separately for each channel in each epoch and then averaged for the two channels. ATR is a non-linear weighted combination of three EEG features, measured at baseline and 1