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Changes in prefrontal activity characterize clinical response in SSRI nonresponders: a pilot study

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Abstract

Previous studies in unipolar depression have shown that early decreases in prefrontal values of the QEEG cordance measure identified responders to pharmacotherapy. These studies have all examined individuals who were drug-free prior to the first physiologic assessment, yet in the clinical management of treatment resistant depression (TRD), many patients undergo changes in treatment without a drug-free interval between treatments. Here, we investigated whether cordance decreases were associated with response in Stage I TRD subjects without wash-out between treatment trials. Awake EEGs were recorded from 12 adults with unipolar depression. Subjects were receiving naturalistic treatment, had failed SSRI monotherapy, and were starting a new treatment prescribed by their treating psychiatrists. EEG data were recorded before starting the new treatment and after approximately 1 week. Six of the 12 subjects responded to treatment after 8–10 weeks. Five of the six responders showed an early cordance decreases, compared with two of the six nonresponders (accurate characterization in 75% of the cases). Consistent with previous treatment trials, decreases in prefrontal cordance differentiated responders from nonresponders in this setting as well. These findings suggest that cordance biomarkers may be a useful tool in effectiveness trials that parallel clinical practices in SSRI nonresponders, and may not require a wash-out period between treatments.

Keywords: Treatment resistant depression; Cordance; EEG; Treatment response; Antidepressant medications; Biomarker

1. Introduction

The clinical management of treatment resistant depression (TRD) involves a series of therapeutic trials of medications, either as monotherapy or in combination (Thase and Rush, 1997; American Psychiatric Association, 2000; Crismon et al., 1999), often without a medication-free ''wash-out'' period between treatments. Once a decision has been made about a next step in treatment, both patient and physician then must wait several weeks to assess clinical improvement with the new regimen. A biomarker that detects a meaningful change in brain physiology prior to significant shifts in clinical symptoms might provide useful data to guide the decision to continue a particular treatment or terminate a trial and move on to the next treatment option.

We have previously reported encouraging data on a quantitative electroencephalographic (QEEG) measure that showed a change in the first week of treatment in the majority of patients who showed clinical response at week eight, and did not show this change in most subjects who failed to respond (Cook et al., 2002). The QEEG cordance measure combines complementary information from absolute and relative power EEG spectral measures to yield values that have

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stronger correlation with regional cerebral perfusion than either measure alone (Leuchter et al., 1999), allowing a physiologic context for the interpretation for the measure.

To have practical use in the clinical management of TRD, a biomarker would need to differentiate reliably between responders and nonresponders without the need for a wash-out period. In previous naturalistic treatment trials (Leuchter et al., 1997; Cook and Leuchter, 2001) and in a randomized controlled clinical trial setting (Cook et al., 2002), subjects who enrolled in the studies had been free of antidepressant medication for at least 2 weeks prior to participation. In this project, we evaluated whether the associations between changes in cordance and treatment outcome could be found in subjects with known SSRI nonresponse and who did not have a wash-out period between trials. Using the parameters advanced by Thase and Rush for multiple levels of resistance to treatment, we studied subjects who fulfilled their criteria for Stage I resistance (''failure of at least one adequate trial of one major class of antidepressant''). We hypothesized that a decrease in prefrontal cordance in the first week of treatment would be associated with clinical response at the end of 8–10 weeks of treatment administered in an open-label, effectiveness trial model.

2. Materials and methods

2.1. Subjects

We studied adults diagnosed with major depressive disorder (MDD) who were receiving naturalistic treatment by psychiatrists at the UCLA Neuropsychiatric Institute and Hospital. All were outpatients with unipolar MDD, with diagnoses confirmed using a structured interview for DSM-IV (First et al., 1994). Subjects were participating in a naturalistic protocol for longitudinal monitoring of brain function in depression. For the present analysis, we included subjects who had failed an adequate trial of monotherapy using a selective serotonin reuptake inhibitor (SSRI), still met diagnostic criteria for a current major depressive episode, and were beginning a new treatment at the recommendation of their treating psychiatrists. We excluded individuals with clinical characteristics that can confound interpretation of the EEG (e.g., history of skull fracture, or concurrent use of benzodiazepine medication). In accordance with principles of the Helsinki Declaration, this protocol had been reviewed and approved by the UCLA Institutional Review Board, and informed consent to participate in this research was obtained from all subjects.

In total, 12 subjects were studied for this pilot project. The group characteristics of these subjects are described in Table 1.

2.2. Experimental procedures

2.2.1. Treatment trial

Treatments were prescribed naturalistically based on the clinical judgment of the treating physician and without direction from a structured protocol or knowledge of physiologic data. Subjects had completed and failed a trial with SSRI monotherapy of at least 6 weeks duration at the time of the first assessment with QEEG and the 17-item Hamilton Depression Rating Scale (HAM-D_{17}) value (fluoxetine $n = 3$; sertraline $n = 3$; paroxetine $n = 1$; citalopram $n = 5$). Subjects then began a new treatment regimen by either (a) switching from one SSRI agent to monotherapy with another agent ($n = 6$), or (b) augmenting the initial treatment with a second agent ($n = 6$). A second QEEG measurement was obtained after approximately one week on the new regimen (mean 7.4 (SD 6.4) days). To permit comparison with prior work with the cordance measure in depression (Cook et al., 2002; Leuchter et al., 2002), we defined clinical response as reduction in final depression severity to a HAM-D score of $\leqslant$10 points; this assessment was made between 8 and 10 weeks of treatment with the new regimen.

2.3. QEEG techniques

2.3.1. Data acquisition

Using procedures employed in our previous reports and summarized here, recordings were made with the

Table 1
Characteristics of subjects

	Responders $n = 6$	Nonresponders $n = 6$	All subjects $n = 12$
Age (years)	56.7 (17.0)	55.5 (12.3)	56.1 (14.2)
Gender ratio (M:F)	2:4	3:3	5:7
Pre-SSRI-trial HAM-D_{17}	14.6 (4.3)	19.3 (3.1)	17.2 (4.3)
Cross-over HAM-D_{17}	13.7 (4.2)	15.7 (5.0)	14.7 (4.5)
Final HAM-D_{17} ($p < 0.001$)	5.8 (3.7)	17.0 (4.3)	11.4 (7.0)

Depression severity was assessed at cross-over from failed treatment to new regimen, and after 8–10 weeks of the new treatment (HAM-D_{17}: 17-item Hamilton Depression Rating Scale). Response groups differed only in post-treatment depression severity (2-tail t tests).