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The Antidepressant Treatment Response (ATR) Index and Treatment Outcomes in a Placebo-controlled Trial of Fluoxetine

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Abstract

Recent research aims at developing a biomarker to predict antidepressant treatment outcomes in Major Depressive Disorder (MDD). The Antidepressant Treatment Response index (ATRindex) has been correlated with response to antidepressant medication (Leuchter et al., 2009a, 2009b) but has not been assessed in a placebo-controlled trial. EEGs were used to calculate ATR-index for 23 randomized MDD subjects to eight weeks of fluoxetine treatment (FLX) 20 mg (n=12) or placebo (n=11). The 17-item Hamilton Depression Rating Scale (HamD17) assessed symptom severity, while a percent change in HamD17 score, endpoint response ($\geq 50\%$ improvement) and remission (HamD17 score ≤ 7) were used to assess ATR-index as a predictor. ATR-index was significantly associated with improvement on FLX ($r = .64$, $p = .01$), with a higher mean ATR-index for FLX responders than non-responders ($t(10) = -2.07$, $p = 0.03$). Receiver Operating Characteristic analysis found a .83 area under the curve ($p = .03$), for ATR-index as a predictor for FLX, while an optimized ATR-index cutoff of 47.3 yielded 100% sensitivity, 66.7% specificity, 75% PPV and 100% NPV. Importantly, ATR-index did not correlate significantly with placebo outcomes. Results extend ATR-index findings to include predictive validity with fluoxetine, suggesting that this biomarker has specificity for drug effects.

Keywords

antidepressant medication; placebo response; biomarker; EEG

Introduction

Pharmacotherapy forms a cornerstone of treatment for Major Depressive Disorder (MDD). Despite the proven efficacy of antidepressant medications, treatment outcome varies greatly among individuals. For example, results of the Sequenced Treatment Outcomes for Relieving Depression (STAR*D) trial found response and remission rates of about 50% and 30%, respectively, during 12 weeks of Level 1 treatment with citalopram (Trivedi et al., 2006). However, following multiple treatment steps, a cumulative 70% of patients who

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Statement of Interest

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remained in the study achieved remission by the end of 12 months (Insel and Wang, 2009). These findings suggest that an individual patient may respond better to one medication than another, an interpretation largely followed in clinical practice where sequential trials of antidepressant medications are used until remission is achieved. Unfortunately, the current trial-and-error approach is often a protracted process during which time patients may experience prolonged suffering and may develop negative treatment expectations (Leuchter et al., 2009c). Time to remission is often extended, in large part due to the typical six- to eight-week waiting period to determine the efficacy of a given medication (Quitkin et al., 2003; Bauer et al., 2007). A biomarker that could predict clinical outcome early in the course of treatment could hasten time to remission by shortening the length of medication trials.

Quantitative electroencephalographic (QEEG) biomarkers of brain functional changes within the first week of antidepressant treatment have shown strong promise as predictors of outcome (Cook et al., 2002; Hunter et al., 2007). The most clinically refined of these is the Antidepressant Treatment Response (ATR) Index, version 4.1 (Aspect Medical Systems; Norwood, MA) (Leuchter et al., 2009a, 2009b). ATR is especially promising for clinical translation both because of its practicality, and its demonstrated ability to predict outcomes at the level of the individual patient. This measure, developed using previous EEG datasets (Cook et al., 2002; Poland et al., 2006; Iosifescu et al., 2009) combines several frontal features from a baseline (pretreatment) EEG and a second EEG after one week of treatment to form an index where higher values are associated with a better chance of response. ATR version 4.1 was evaluated in the Biomarkers for Rapid Identification of Treatment Effectiveness in Major Depression (BRITE-MD) trial, an open-label randomized study of 220 evaluable subjects, where it predicted escitalopram (ESC) response and remission with 74% accuracy (Leuchter et al., 2009a). Analyses of other treatment arms in the same trial revealed that ATR predicted differential response to ESC versus bupropion (BUP) (Leuchter et al., 2009b). That is, a high ATR index during an initial week of ESC treatment predicted response to ESC, whereas low ATR during one week of ESC treatment predicted poor response to ESC, but positive response to treatment with BUP. An independent study of a prior version of ATR in 82 subjects treated naturalistically primarily with a Selective Serotonin Reuptake Inhibitor (SSRI) antidepressant or the mixed reuptake inhibitor venlafaxine found that the ATR value obtained in the first week of treatment predicted response to the given medication with 70% overall accuracy (Iosifescu et al., 2009).

Whereas there is good evidence to corroborate that ATR predicts medication response, one question yet to be addressed is how ATR relates to placebo response. Because of the ubiquitous high rates of placebo response observed in clinical trials in MDD, it is likely that some portion of response in medication-treated subjects is driven by non-specific (i.e. “placebo”) effects. From a clinical perspective, it would be important to know whether the relationship between ATR and clinical outcomes is explained by placebo effects, or whether ATR indeed predicts medication-specific outcomes. Here we assessed the relationship between ATR values and treatment response to fluoxetine (FLX) and placebo in the context of a double-blinded randomized controlled trial in MDD. We hypothesized that ATR values would be higher among FLX responders as compared to FLX non-responders. If ATR is a marker of specific treatment effects we would expect higher values on this index to predict response to medication but not placebo.

Methods

Subjects

This report is based on 23 subjects who underwent QEEG recordings and who completed a randomized placebo-controlled trial of FLX for MDD. Subjects were recruited from the

local community as well as from outpatient clinics of the UCLA Neuropsychiatric Hospital. Each enrollee met DSM-IV criteria for MDD and had a HamD₁₇ score ≥ 16 at entry. Subjects were free of any medication known to affect brain function (except for the study medication) throughout the study and for one week prior. All investigations were conducted in accordance with the Declaration of Helsinki. Procedures were approved by the UCLA Institutional Review Board and subjects provided written informed consent before any experimental procedures were performed.

Study Design

Twenty-four subjects were randomly assigned to eight weeks of double-blinded treatment with FLX 20 mg, ($n = 13$) or placebo ($n = 11$) following a one-week single-blinded placebo lead-in. Symptoms were monitored and HamD₁₇ scores were obtained at baseline, end of placebo lead-in, 48 hours after start of randomized treatment, and at weekly visits over the eight weeks of randomized treatment. Scheduled visits included 15–25 minutes of unstructured counseling and problem-solving assistance in order to address safety concerns involved with dispensing placebo alone to depressed individuals. Clinical response ($\geq 50\%$ improvement) and remission (final HamD₁₇ score ≤ 7) status was examined for each subject at week eight. Associations between ATR and clinical outcomes were analyzed separately for those subjects treated with FLX or placebo.

QEEG methods

EEG recordings were performed using thirty-five recording electrodes positioned with an electrode cap (ElectroCap; Eaton, OH) using an extended International 10–20 System. Recordings were obtained while subjects rested in the eyes-closed, maximally alert state in a sound-attenuated room with subdued lighting, using the QND system (Neurodata, Inc.; Pasadena, CA) with a Pz reference montage. Eye movements were monitored using right infraorbital and left outer canthus electrodes. Data were digitized on-line at 256 samples/channel/sec with a high-frequency filter of 70 Hz and a low-frequency filter of 0.3 Hz, and were reformatted off-line by amplitude subtraction to construct a bipolar electrode pair montage. An EEG technologist blinded to subject identity and treatment condition selected for processing the first 20–32 seconds of artifact-free data. An independent blinded technologist confirmed the selection prior to processing.

ATR

To compute an ATR value for each subject, we examined brain functional measures from EEG recordings taken at two time points: at baseline, and at the end of one week of randomized treatment with FLX or placebo. ATR values were calculated from artifact-free maximally awake EEG recorded from ear-referenced channels A1-Fpz, and A2-Fpz. Power spectra of the EEG were calculated separately for each channel in 2-second epochs and then averaged for the two channels. ATR is a non-linear weighted combination of three EEG features (measured at baseline and after 1 week of antidepressant treatment) that previously were identified as being associated with antidepressant outcome: relative power in a combined theta and alpha range (3–12 Hz), absolute power in the alpha1 band (8.5–12 Hz), and absolute power in the alpha2 band (9–11.5 Hz) (Cook et al., 2002; Iosifescu et al., 2006; Poland et al., 2006). Relative combined theta and alpha power (3–12 Hz) is calculated as the ratio of absolute combined theta and alpha power divided by total power (2–20 Hz). ATR combines relative theta and alpha power at week 1, and the difference between alpha1 power at baseline and alpha2 power at week 1. The ATR index is scaled from 0 (low probability) to 100 (high probability) of response. Leuchter et al., 2009a Appendix A contains further details regarding ATR calculations.

Data Analysis

Statistical analyses were performed using PASW statistics software, version 17 (SPSS, Inc.; Chicago, IL). We examined bivariate correlations between ATR value and percent change in HamD₁₇ scores from baseline to week eight, separately for FLX and placebo groups. Additionally, between groups t-tests were used to compare ATR values between responders ($\geq 50\%$ response) and non-responders, and between remitters (final HamD₁₇ ≤ 7) and non-remitters, in the two treatment conditions. Following a significant ATR difference between responders vs. non-responders, or remitters vs. non-remitters for either treatment, Receiver Operating Characteristic (ROC) analyses were conducted to assess overall predictive accuracy and to determine an optimal ATR cutpoint. Fisher's exact test was used to compare the accuracy of an ATR cutpoint optimized for the present data, to the accuracy of the optimized ATR cutpoint of 58.6 that was determined in the prior report on ESC (Leuchter et al., 2009a). Positive predictive value (PPV) was calculated as (number of true positives)/(number of true positives + number false positives); negative predictive value (NPV) was calculated as (number of true negatives)/(number of true negatives + number false negatives). Finally, we also conducted stepwise logistic regression analyses to compare the predictive accuracy of ATR and clinical features. Significance levels were set at $p < .05$ single-tailed for directional hypotheses (i.e., higher ATR associated with FLX response).

Results

Subject Characteristics and Clinical Outcomes

Of 24 subjects who completed the protocol, 23 had usable EEG with which to calculate ATR. Table 1 shows clinical and demographic characteristics of the 23 subjects on whom we report. Medication-versus placebo-group subjects did not differ significantly on age, gender, baseline severity, or history of prior treatment. Medication subjects showed a 50% rate of response and a 25% rate of remission. In the placebo group, rates of response and remission were 54.5% and 27.3%, respectively. Chi-square analyses did not reveal any significant difference in response or remission rates between FLX- and placebo-treated subjects.

ATR and Treatment Outcomes

FLX Outcomes—ATR was positively associated with percent change (improvement) in HamD₁₇ score among FLX-treated subjects ($r = .64$, $p = .01$, 1-tailed) (Figure 1). Between-group t-tests found significantly higher ATR values in medication responders versus non-responders ($t_{(10)} = -2.07$, $p = 0.03$, 1-tailed), and numerically but not significantly higher ATR in medication remitters versus non-remitters (Table 2). ROC analyses examining ATR as a predictor of response found .83 area under the curve (AUC) ($p = .03$) (Figure 2). An optimized ATR cutoff of 47.3 yielded 100% sensitivity, 66.7% specificity, 75% PPV and 100% NPV.

We used Fisher's exact test to compare the accuracy of the optimized threshold derived from these data, 47.3, to the optimized threshold of 58.6 determined from the prior report of ESC⁸. The distribution of correct vs. incorrect decisions when applying an ATR cutpoint of 47.3 vs. 58.6 (2×2 contingency table) was not statistically significant (Fisher's exact $p = 1.0$). Thus the accuracy at these ATR cutoff thresholds was not significantly different.

As basis for comparison with the ATR predictor, we examined the clinical features, including baseline illness severity and early improvement, as predictors of week eight improvement in the FLX group. Baseline HamD₁₇ score was not significantly associated with outcome ($r = -.38$, $p = .23$, two-tailed, N.S.) whereas one-week change in HamD₁₇ score showed a one-tailed trend relationship to final outcome in the predicted direction, i.e.,

improvement at week one was associated with improvement at week eight ($r = .49$, $p = .05$, one-tailed). We conducted forward stepwise linear regression to determine whether 'week one improvement' might add to ATR in modeling clinical improvement at week eight. This analysis identified only ATR ($R^2 = .42$, $p = .02$) as a significant predictor of improvement; week one symptom change did not enter the model.

Placebo Outcomes—There was no significant correlation between ATR and clinical improvement in placebo subjects ($r = -.33$, $p = 0.32$, 2-tailed, N.S.). ATR values for placebo outcome groups are shown in Table 2. Neither baseline severity, nor early symptom improvement predicted placebo outcomes.

Discussion

This is the first report to examine the ATR index in a randomized placebo-controlled trial. Consistent with the results of prior reports (Iosifescu et al., 2006; Leuchter et al., 2009a, 2009b), higher ATR values were significantly associated with greater improvement and greater likelihood of response during antidepressant treatment. Importantly, ATR was not found to predict response to placebo, suggesting that this biomarker reflects specific treatment effects.

Results of this study extend prior work to assess ATR version 4.1 as a predictor of response to FLX. Given results of the prior study of ATR in ESC-treated subjects (Leuchter et al., 2009a), it is not surprising that ATR predicted response to FLX, a medication with a similar (i.e., SSRI) mechanism of action. However, there were several differences in the findings across these studies. First, although ATR predicted response ($\geq 50\%$ improvement) in both the prior report of ESC and the present study of FLX, ATR did not predict remission (final HamD₁₇ score ≤ 7) to FLX. Second, whereas the ESC report found that symptom improvement at one week added significantly to ATR in an overall model to predict clinical outcome, week one symptom improvement did not add predictive value over and above that of ATR in predicting response to FLX in our subjects. These differences could be due to the specific medication used, or to differences in study design such as the inclusion of a 1-week placebo lead-in in the present study. Lastly, the optimized ATR cutoff value in the present study was numerically lower than the optimized cutoff that was determined in the BRITE-MD study of ESC. However, when we applied the prior ESC cutoff (58.6) to the present data, we found that it did not yield statistically different accuracy in predicting response as compared to optimized FLX cutoff of 47.3. Therefore we cannot conclude that one should use a different cutoff for FLX than for ESC. Further studies are needed to determine whether the same ATR cutoff value could be used for an entire class of antidepressants, or if the appropriate ATR value would vary based on individual antidepressant medications.

The present study did not find an association between ATR and placebo response on any of the outcomes examined including response or remission at endpoint, or percent improvement over the course of the trial. This observation is consistent with the view of ATR as a marker of specific treatment effects. Despite no significant difference in the rates of response and remission between medication and placebo subjects, the ATR index was predictive of response to the antidepressant only. This observation suggests that ATR detects early *medication effects* on brain physiology that are related to ultimate clinical outcomes. Interestingly, we observed that placebo responders had numerically lower ATR values as compared to placebo non-responders. Though not statistically significant, this opposite relationship is consonant with the idea that improvement on antidepressant medication and placebo may involve different mechanisms of action. A previous study found that individuals who responded to placebo treatment displayed prefrontal functional EEG changes (QEEG cordance) that were distinct from those associated with improvement on

antidepressant medication (Leuchter et al., 2002). Although there may indeed be overlap in some brain mechanisms that support response to antidepressant medications and placebo (Mayberg et al., 2002), the present findings suggest that ATR detects neurophysiologic changes that are unique to medication response. This raises the question of potential relationships between ATR and other specific treatments for MDD (e.g., electroconvulsive therapy, transcranial magnetic stimulation, cognitive-behavioral therapy). Future work might address applications of ATR to other specific treatments, but these interventions are likely to involve distinct time courses and neurophysiologic processes.

Results of this study further support ATR as a viable biomarker of antidepressant treatment response with the potential for clinical application. The ability to accurately predict response to a specific medication within the first week of treatment could lead to faster overall time to response for patients who might otherwise suffer long sequential medication trials before finding a medication that is effective (Leuchter et al., 2009c). Results of this study should be viewed alongside its limitations including small sample size and retrospective analyses. Next steps in the testing and development of this putative biomarker should be to prospectively examine ATR as a predictor of response among subjects randomly assigned to placebo or one of a number of different antidepressant medications with various mechanisms of action. Larger studies of this kind would allow for direct comparison of the ATR index across treatments and for further development of cutoff scores to be used in clinical practice.

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Andrew Leuchter, M.D. has provided scientific consultation or served on advisory boards for Aspect Medical Systems, Bristol-Myers Squibb, Eli Lilly and Company, Merck & Co., Otsuka Pharmaceuticals, and Pfizer. He has served on a speaker's bureau for Bristol-Myers Squibb, Eli Lilly and Company, Otsuka Pharmaceuticals, and Wyeth-Ayerst Pharmaceuticals. He has received research/grant support from the National Institute of Mental Health, the National Center for Complementary and Alternative Medicine, Aspect Medical Systems, Eli Lilly and Company, Wyeth-Ayerst Pharmaceuticals, Merck & Co., Pfizer, Sepracor, Vivometrics, and MedAvante. He also is a former equity shareholder in Aspect Medical Systems.

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Figure 1.
ATR as predictor of percent change in HamD₁₇ score in fluoxetine subjects.

Figure 2. Receiver Operating Characteristic (ROC) curves examining ATR as a predictor of response in MDD subjects treated with fluoxetine.

Table 1

Baseline Characteristics

Metric	All subjects (n=23)	Study Arm		Statistic and p-value (2-tailed)
		FLX (n=12)	PBO (n=11)	
Age (years)	40.43 (± 11.74)	43.41 (± 14.14)	37.18 (± 7.82)	$t(21) = -1.29$, $p=0.21$
Gender (% female)	65.2	75	54.5	$\chi^2(1)=1.06$, $p=0.30$
Ham-D 17	22.00 (± 4.09)	23.17 (± 4.26)	20.73 (± 3.66)	$t(21) = -1.47$, $p=0.16$
Previous Treatment (% yes)	43.5	41.7	45.5	$\chi^2(1)=0.03$, $p=0.86$

Table 2

ATR Clinical Characteristics by treatment and outcome group

Treatment arm	Subject group	Mean age	M:F ratio	Mean initial Ham-D	Mean final Ham-D	% change in Ham-D from baseline to week 1	Mean ATR value
FLX	All subjects (n=12)	43.41 (±14.14)	3:9	23.17 (±4.26)	13.5 (±8.25)	26.03 (±22.26)	52.30 (±16.82)
	Responders (n=6)	41.83 (±15.38)	2:4	21.17 (±2.40)	6.67 (±4.13)	40.71 (±21.26) ^a	61.10 (±12.16) ^b
	Non-responders (n=6)	45.00(±14.04)	1:5	25.17 (±4.96)	20.33 (±4.55)	11.34 (±10.99)	43.49 (±16.99)
	Remitters (n=3)	30.33 (±8.62)	1:2	21.67 (±2.08)	3.33 (±2.52)	37.82 (±14.77)	63.01 (±10.53)
	Non-Remitters (n=9)	47.78 (±13.07)	2:7	23.67 (±4.77)	16.89 (±6.35)	22.10 (±23.61)	48.72 (±17.43)
PBO	All subjects (n=11)	37.18 (±7.82)	5:6	20.73 (±3.66)	12.09 (±8.23)	30.04 (±26.76)	55.64 (±7.07)
	Responders (n=6)	34.00 (±8.15)	3:3	19.33 (±2.66)	6.17 (±3.87)	35.30 (±30.85)	52.24 (±7.09)
	Non-responders (n=5)	41.00(±6.04)	2:3	22.40 (±4.28)	19.20 (±5.89)	23.73 (±22.56)	59.71 (±4.91)
	Remitters (n=3)	32.67 (±9.81)	3:0	17.33 (±1.15)	3.00 (±2.65)	28.7 (±43.42)	52.91 (±3.86)
	Non-Remitters (n=8)	38.88 (±6.92)	2:6	22.00 (±3.46)	15.5 (±6.78)	30.54 (±21.98)	56.66 (±7.93)

^a Responders different from non-responders, p = .007 (one-tailed)

^b Responders different from non-responders, p = .03 (one-tailed)