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Authors

Cook, Ian
Hunter, Aimee
Caudill, Marissa
et al.

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Prospective testing of a neurophysiologic biomarker for treatment decisions in major depressive disorder: the PRISE-MD trial

Ian A. Cook, MD[a,b], **Aimee M. Hunter, PhD**[a], **Marissa M. Caudill, MD, PhD**[a], **Michelle J. Abrams, RN**[a], **Andrew F. Leuchter, MD**[*,a]

[a]Department of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and Human Behavior, David Geffen School of Medicine at UCLA, 760 Westwood Plaza, Los Angeles, CA, USA.

[b]Department of Bioengineering, Henry Samueli School of Engineering and Applied Science at UCLA, 410 Westwood Plaza, Los Angeles, CA, USA.

Abstract

[*]Corresponding author: Andrew Leuchter, MD. Semel Institute for Neuroscience and Human Behavior at UCLA. 760 Westwood Plaza. Los Angeles CA 90024. afl@ucla.edu. P: 310-825-0207.

Management of Major Depressive Disorder (MDD) might be improved by a biomarker to predict whether a selected medication is likely to lead to remission. We previously reported on a quantitative electroencephalogram-based biomarker, the Antidepressant Treatment Response (ATR) index, that integrated recordings at baseline and after one week of treatment. The present study prospectively tested whether treatment directed by the biomarker increased the likelihood of remission; we hypothesized that continued treatment with a drug predicted to lead to remission (i.e., high ATR values) would be associated with better outcomes than if the drug was predicted not to lead to remission (i.e., low ATR values). We enrolled 180 adult outpatients with unipolar MDD from the community. After one week of escitalopram treatment to determine the biomarker, stratified randomization (high vs. low ATR) was used to assign subjects to either continued escitalopram or a switch to bupropion as a blinded control condition, for seven additional weeks. For the 73 evaluable subjects assigned to continued escitalopram treatment, the remission rate was significantly higher for those in whom ATR had predicted remission versus non-remission (60.4% vs. 30.0%, respectively, p=0.01). Accuracy was enhanced by combining 1-week depressive symptom change with ATR (68.6% vs 28.9%). This prospective validation study supports further development of the ATR biomarker, alone or together with early symptom change, to improve care by identifying individuals unlikely to remit with their current treatment, and support the decision to change treatment after one week rather than after failing a full, prolonged course of medication.

Keywords

Major Depressive Disorder; Antidepressants; EEG; Drug Response Biomarkers

INTRODUCTION

Best practices for managing Major Depressive Disorder (MDD) call for systematic prescription of antidepressant agents in a sequence of trials, each typically lasting 6 to 12 weeks, in order to reach remission (Gelenberg et al., 2010; Lam et al., 2016). The landmark STAR*D trial exemplified this approach (Warden et al., 2007a). A limitation of this trial-and-error approach is the time needed to determine that a medication choice has been incorrect, as half of those who will remit with a given treatment do so quickly (within 6 weeks) while half take longer (6 to 12 weeks) (Trivedi et al., 2006). The STAR*D trial also demonstrated that many patients abandon treatment during this lengthy process (Warden et al., 2007a). A biomarker that could give an early prediction of treatment effectiveness could shorten the duration of this sequential process with potential to improve outcomes.

In prior studies of neurophysiologic biomarkers, changes in the quantitative electroencephalogram (qEEG) have been reported to be predictive of outcomes, particularly measures in the theta band, over the prefrontal region, and comparing baseline activity with that after one week of treatment (i.e., the "how, where, and when" of a predictor) (Leuchter et al., 2014; Cook, 2008; Bares et al., 2010). These approaches required data from numerous electrodes placed over the entire head, however, with methods needing specialized expertise. Functional neuroimaging has revealed that the far prefrontal region of the brain constitutes a "dorsal nexus," reflecting brain functional connectivity perturbations in MDD (Sheline et al., 2010). Placing a very limited number of electrodes over this region has been shown to

provide unique information about brain function in MDD (Cook et al., 2014). This type of focused electrode array could facilitate a clinically-useful biomarker that could be easily integrated into clinical practice.

Previous reports described the rationale for and development of a predictive biomarker that utilized a focused array of three electrodes (Leuchter et al., 2009a, 2009b). This biomarker, the Antidepressant Treatment Response (ATR) index, was constructed using qEEG data from prior studies, and in a new trial, successfully differentiated between end-of-trial remitters and non-remitters using data at baseline and week 1 of treatment (Leuchter et al., 2009a, 2009b). That study found that high ATR values ("ATR+" status) were associated with remission on escitalopram, while low values ("ATR−") were associated with poor outcomes with continued escitalopram treatment. Prediction was significantly greater than that achieved with clinical or demographic variables, although ATR accuracy was increased by the inclusion of one week change of depression severity in the model. The present project, "Personalized Response Indicators of SSRI Effectiveness in Major Depression" (PRISE-MD), builds on this past work as a prospective validation study with ATR to test the usefulness of this qEEG biomarker in deciding whether or not to continue treatment with a selective serotonin reuptake inhibitor (SSRI) antidepressant after a week of administration. We hypothesized that SSRI treatment consistent with the biomarker prediction would be associated with significantly better outcomes than SSRI treatment not consistent with the biomarker. We also examined whether the continue-or-switch medication decision could be enhanced by the inclusion of previously reported clinical outcome predictors, consistent with the central tenet of precision medicine of the right treatment for the right patient at the right time.

MATERIALS AND METHODS

Study Design

A randomized clinical trial design was employed (Figure 1), with parallel groups receiving escitalopram (ESC) or bupropion (BUP). ESC was selected as a prototypical SSRI, and BUP was selected as a control comparator agent with minimal serotonergic impact, but with both being widely-prescribed first-line evidence-based treatments[1] to maintain clinical equipoise and blinding to treatment. All subjects started with one week of single-blind ESC for measuring the biomarker, and then were randomized to continue on ESC or switch to BUP under double-blind conditions for the remaining seven weeks. Randomization was stratified: approximately half of ATR+ subjects, and likewise, half of ATR− subjects, were randomized to each medication. Allocations were determined using a stratified randomization table constructed in Excel (Microsoft, Inc., Redmond WA), with all clinical staff blinded to ATR value and whether assignment was concordant with the biomarker for each subject. An independent staff member, who had no interactions with the staff or subjects for this project, consulted the table and relayed the assignment (ESC or BUP) to the research pharmacy; subjects and clinical staff remained blinded to the biomarker status throughout the study (concordant or contrary to the biomarker), though they were aware of which medication had been assigned. This report focuses on findings with subjects assigned to continuing ESC to

test our hypotheses. The study was neither designed nor adequately powered to test prediction of outcome with the control comparator BUP.

The primary endpoint was pre-defined as the week 7 visit for ESC subjects, reflecting 7 weeks of continuous ESC administration. In the BUP group, the endpoint was week 8 (7 weeks of continuous BUP). The study was designed to have adequate statistical power to evaluate outcomes with ESC, with a null hypothesis that outcomes with ESC treatment would not be related to biomarker stratification, i.e., not differ between ATR+ and ATR− subjects. Because pilot data (Leuchter et al., 2009a, 2009b) had demonstrated a medium-to-large effect size for ESC, we designed our trial with a target randomized sample of N=172 to detect a medium size effect (w=0.4, 80% power, alpha 0.05).

In accordance with principles of the Helsinki Declaration, all protocols were reviewed and approved by the UCLA Institutional Review Board, and all subjects provided written informed consent. In the consent process, the teach-back method (Agency for Healthcare Research and Quality, 2019) was employed to ensure that subjects demonstrated decision-making capability and understanding of the elements of participation, including the feature that all subjects would be receiving antidepressant medication during participation. This project was registered at ClinicalTrials.gov as "Personalized Indicators for Predicting Response to SSRI Treatment in Major Depression (The PRISE-MD Study)" NCT00917059.

Subjects

Subjects were recruited from the community (e.g. via online ads) and seen in an outpatient academic medical center. A total of 274 adults were screened, 214 consented, and 180 subjects met criteria and enrolled for randomization. Subjects were required to have been free of any psychoactive medications for at least two weeks before entering; to be between 21 and 75 years of age; to meet criteria for a DSM-IV diagnosis of MDD based on the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 2008); and to score at least 12 on the Quick Inventory of Depressive Symptomatology (QIDS-SR16) (Rush et al., 2003) the same criteria as the BRITE-MD study (Leuchter et al., 2009a, 2009b).

Subjects were excluded for being in stable remission on current medication(s) or for having any unstable medical illnesses that could prevent trial completion. Other exclusion criteria included: anorexia nervosa, bulimia nervosa, obsessive-compulsive disorder; any cognitive disorder, psychotic disorder, bipolar disorder, or major depression with psychotic features; substance abuse or dependence within the preceding nine months; ECT within the prior six months; starting psychotherapy for depression within the prior two months; pregnancy or breastfeeding; requiring hospitalization (e.g., imminent danger); use of medications known to affect brain function (e.g., benzodiazepines, anticonvulsants, sedating antihistamines).

Assessments

Baseline assessments included the MINI and QIDS-SR for eligibility determination. The 17-item Hamilton Depression rating scale (HDRS) (Hamilton, 1960) was assessed at baseline along with the 30-item Inventory of Depressive Symptomatology (IDS-SR). Over the 8-week trial, subjects were evaluated weekly in office for symptom changes and side effects.

The primary efficacy metric was the HDRS. Side effects were monitored with the SAFTEE-SI instrument (Levine and Schooler, 1986).

EEG Biomarker

Subjects underwent in-office qEEG recordings (~15 minutes) at baseline and after one week of single-blind daily ESC. An automated qEEG system (Covidien, Ltd., Norwood, MA) selected artifact-free epochs and performed spectral analysis to determine power values using data from FT7-FPz and FT8-FPz channels (Figure 3). The same ATR software was used here and in the BRITE-MD trial (Leuchter et al., 2009a, 2009b; Cook et al., 2013). In that earlier trial, signals in A1-FPz and A2-FPz channels had been used to compute ATR values but many subjects in that study were excluded due to electrocardiogram artifact contamination of the qEEG signals involving ear electrodes (A1, A2). Frontotemporal electrodes were used PRISE-MD to reduce this problem, because signals at those electrode locations are less influenced by the bulk volume electrical conduction of ECG signals through the tissues of the neck. Using the same qEEG epochs, ATR derived from ear-reference channels was significantly correlated with ATR from frontotemporal channels (R^2 = 0.105, p<0.0001). The ATR cutpoint used in this analysis (ATR+ for values 46.2, ATR− for lower values) was based upon analysis of recordings from these frontotemporal channels. The Supplement shows the details of a comparison of ATR from A1-A2 vs FT7-FT8 electrodes.

As in BRITE-MD, a nonlinear algorithm combined power values to compute ATR (Leuchter et al., 2009a, 2009b; Cook et al., 2013). The three qEEG features incorporated into ATR were relative combined theta and alpha power (3–12 Hz), alpha1 absolute power (8.5–12 Hz), and alpha2 absolute power (9–11.5 Hz). Relative combined theta and alpha power (3–12 Hz) was calculated as the ratio of absolute combined theta and alpha power, divided by total power (2–20 Hz). ATR (version 4.1) employed a weighted combination of relative theta and alpha power at week 1, and the difference between alpha1 power at baseline and alpha2 power at week 1, scaled to range from 0 (low probability of remission) to 100 (high probability). This is the same computation of the ATR values as was used in the earlier studies (the same software was used in both projects); the electrode locations have been shifted to reduce exclusion of subjects for ECG-contamination of the ear electrodes.

Treatment

All subjects received an initial week of single-blind ESC (10 mg daily) to determine ATR. Double-blind treatment with daily dosing of either ESC (10 mg) or BUP (150 mg) commenced immediately following the week of ESC (Figure 1). Subjects were unblinded after final assessments to facilitate their further treatment.

Statistical Analyses

Data were analyzed from parallel groups with SPSS software (version 24, IBM, Armonk NY) using step-wise logistic regression models with backwards conditional selection (Pin=0.05, Pout = 0.10), chi square, and t-test 2-tail statistics, as well as receiver operating characteristic (ROC) curve analysis and jack-knife cross-validation. Our primary endpoint

was reached at the week 7 visit for ESC subjects and at the week 8 visit for the BUP subjects.

RESULTS

Subjects

Of the 214 adults who consented to participate, 34 failed to meet entry criteria. Of the 180 subjects who started the single-blind ESC week, 40 dropped out before randomization, with none attributing this to the qEEG test. Of the 140 subjects randomized to treatment, 133 completed at least 4 weeks of the trial and had evaluable clinical data: 75 received ESC and 58 received BUP under ATR-stratified randomization. Of the clinically evaluable sample, 73 of 75 ESC subjects, and 56 of 58 BUP subjects had usable EEG data for inclusion in the ATR predictor analysis (Figure 2).

Subjects randomized to ESC vs. BUP in the ATR predictor analysis did not differ on age or baseline severity but did on gender mix (ESC 66% females vs. BUP 46% females; chi sq 6.37 p<0.02). ESC subjects classified as 'ATR+' (n=43) vs. 'ATR−' (n=30) did not differ significantly on age (37.6 (11.1 sd) years vs 39.6 (13.8 sd)), gender (28F:15M vs 20F:10M), or initial depression severity (HDRS 21.1 (3.9) vs 22.8 (4.3)). Of the 56 BUP subjects, those classified as 'ATR+' (n=28) vs. 'ATR−' (n=28) did not differ on age (37.2 (12.8) years vs 40.0 (14.7)), gender (11F:17M vs. 15F:13M) or initial depression severity (23.5 (5.6) vs. 21.4 (3.8)).

Clinical Results

For the 73 ESC subjects, clinical remission (HDRS 7) was achieved by 39.7% of the sample at week 6, by 47.9% at week 7, and by 52.1% at week 8. The week 7 value was the *a priori* endpoint for ESC subjects (to preserve blinding), and was used for our analyses. For the 56 BUP subjects, 40.0% achieved remission at week 6 (5 weeks of BUP), 41.8% at week 7 (6 weeks of BUP), and 52.7% at week 8 (7 weeks of BUP). Side effects were in line with those anticipated for these medications, based upon the product package labeling.

ATR Biomarker Findings

ATR was not significantly related to age, gender, baseline severity, or symptom change at 1 week, but was related to clinical outcome. As a test of our primary hypothesis, biomarker category (ATR+ vs. ATR−) was significantly related to remission status in subjects treated with ESC, with 60.5% ATR+ vs. 30.0% ATR− subjects achieving remission (Chi square 6.572, p=0.010). ROC curve analysis revealed 0.635 area under the curve (AUC) (95% CI 0.506 – 0.763, p=0.048) (Figure 3). Using a cutpoint of 46.2, ATR predicted remission with test sensitivity 74.3%, specificity 55.3%, positive predictive value 60.5%, negative predictive value 70.0%, and overall accuracy 64.4%. Within the ESC group, remitters had significantly higher ATR values than non-remitters (50.9 (10.2 sd n=35) vs. 45.8 (11.3 sd n=38), t(71)=2.02, p=0.048). Remitters did not differ significantly with regard to HDRS symptom improvement at one week (remitters 6.69 (4.30 sd) vs nonremitters 4.71 (4.77 sd) point improvement).

Jack-knife cross-validation was performed with the ESC group to estimate stability of the model. Classification matrices were computed for all permutations of subject pool with individual subjects successively removed, with accuracies in the narrow range of 63.9% to 65.3% (mean 64.4%, sd 0.7, 95% CI 64.2–64.6) and chi square statistics from 6.512 to 8.109 (mean 7.00 sd 0.60).

Although the trial was not designed with statistical power to test hypotheses related to BUP, ATR values were not different between Week 8 BUP remitters (n=29) and non-remitters (n=26) (48.3 (11.7 sd) vs. 48.4 (12.2 sd)) t=0.033 2-tail p=0.974). Remission rates among BUP subjects did not differ based on ATR value (53.6% for ATR+ subjects vs 50.0% for ATR- subjects). ROC analyses found no predictive relationship between the ESC-derived ATR value and remission with BUP (AUC 0.520 (SE 0.080) p=0.80).

As in the BRITE-MD trial, we examined hybrid prediction models incorporating features that clinicians could use to inform the continue-or-switch decision. By adding early symptom change to ATR in a multivariate logistic regression, the combined predictor equation was stronger than ATR alone (chi sq 11.78, p=0.003): of 35 remitters, 24 would have been predicted to remit, and of 38 non-remitters, 27 would have been predicted not to remit (overall accuracy 69.9%). With this hybrid model, subjects "correctly" assigned to ESC had a 68.6% chance of remission, while those "incorrectly" continuing on ESC had 28.9% likelihood of remission.

DISCUSSION

In our subject pool, biomarker-guided treatment selection led to a higher remission rate that was statistically significant and clinically meaningful. Subjects assigned to continued SSRI treatment concordant with biomarker status were significantly more likely to enter remission than those assigned contrary to biomarker guidance. Individuals who had been randomized to ESC and predicted to do well achieved a significantly higher rate of remission than those randomized to ESC who were not predicted to remit and, as has been previously reported, combining the qEEG biomarker with early symptom changes yielded even greater accuracy in predicting remission. Jackknife cross-validation showed that the predictor was stable and reproducible in our dataset. While symptom improvement at one week of treatment was not predictive of eventual remission, inclusion of early symptom change along with ATR in a hybrid model yielded an improved prediction of outcome over ATR alone.

Our findings suggest that a qEEG-based biomarker could be integrated into a modified clinical treatment paradigm: an initial medication could be selected, a baseline qEEG recorded and symptom severity measured, and after a week of taking that agent, a follow-up qEEG recording would generate a biomarker indicating whether continued treatment with that agent was likely to lead to remission and early symptom change would be scored. In this framework, a treatment decision could be made at the one-week point using physiologic and clinical data together, rather than after many weeks of expectant observation. Shortening trial time from months to a single week could accelerate identification of a successful treatment, shorten episode duration, and reduce disability. Subjects endorsed the acceptability of qEEG recording, and we found a 97% success rate of useable EEG data

using frontotemporal focused-array electrodes, indicating that this technique could be practical for routine use, once subjected to out-of-sample validation and direct replication with additional studies, as critically noted by Widge et al. (2019).

It is noteworthy that, in this study, the ATR biomarker predicted outcomes for the drug used to assess the biomarker, but not for the comparator treatment. Subjects in the earlier BRITE-MD trial with low ATR values who received BUP had better outcomes than those with high ATR values, but this relationship was not found in the current study. It is not clear why the ESC-based ATR status was related to BUP outcomes in BRITE-MD, but not in PRISE-MD. This could reflect differences in the subjects, in montage, in randomization (simple vs stratified), or other unknown factors. Future studies should examine other pairings of test- and treatment-drug to determine whether outcome prediction is specific to the test drug, generalizes to a mechanistic medication class (i.e., does a biomarker measured with one SSRI predict outcome to other SSRIs), or has a reliable relationship to out-of-class changes in treatment. Future studies could also consider what factors may influence the index besides antidepressant medication effects, and examine different threshold values (ATR+/−) that may pertain to different populations. Given the modest ROC parameters we observed, further development of the underlying ATR algorithm might also be undertaken, using additional data for training the algorithm and refining cutpoints.

The ATR biomarker was derived empirically from historical datasets and was first tested prospectively in the BRITE-MD study (Leuchter et al., 2009a, 2009b). ATR is based upon integration of alpha and theta power measurements immediately before and one week after starting treatment. As context, much work has focused on degrees of asymmetry in alpha power to predict treatment outcome (Bruder et al., 1999, 2001, 2004, 2008; Jaworska et al., 2012, 2014; Tenke et al., 2011; Arns et al., 2016). Other studies have considered alpha activity as related to arousal regulation (Schmidt et al., 2017; Ulke et al., 2019), or have considered combinations of alpha and theta activity, either in models incorporating prefrontal theta cordance and occipital alpha asymmetry (Bares et al, 2019) or in a machine-learning paradigm using source localization as well as surface signals (Jaworska et al, 2019). Still other work has examined the loudness dependent auditory evoked potential (LDAEP), also called the intensity dependence of cortical auditory evoked potentials (IDAP) as an outcome predictor (Linka et al., 2004, 2005). The IDAP is an N100 event related potential and therefore represents evoked power in the alpha range. While many reports have indicated that intensity of alpha oscillations before and during treatment are related to treatment outcome, the physiologic basis for this association is incompletely understood. Our group has reported that treatment with ESC alters the ratio of delta+theta (2.5 – 8 Hz) to alpha activity in the prefrontal region, and is a specific predictor of remission with ESC but not placebo (Leuchter et al., 2016). We theorized that shifts in prefrontal rhythmic activity in the 2.5 – 12 Hz range may reflect the influence of serotonergic reuptake inhibition in the dorsomedial thalamic nucleus (DM) (Leuchter et al., 2015). Changes in resting state (as well as evoked) delta, theta, and alpha activity may therefore predict treatment outcome through measurement of the resolution of a state of "thalamocortical dysrhythmia" (TCD), namely, highly resonant rhythmic oscillations in thalamocortical circuits involving the prefrontal region (Leuchter et al., 2014, 2015, 2016; Llinás et al., 1999; Fröhlich, 2015). This theory is consistent with the finding that the prefrontal midline electrode (FPz), which overlies cortex

that is regulated by the DM, provides unique information that distinguishes MDD subjects from healthy controls (Cook et al., 2014). This same electrode constitutes a hub of increased neurophysiologic connectivity in subjects with MDD (Leuchter et al., 2012) and overlies structures predictive of treatment outcomes in MDD and other mood, anxiety, and substance use disorders (Etkin et al., 2011; Ball et al., 2017; Moeller and Paulus, 2017; Pizzagalli et al., 2018). Future studies could more directly examine the actions of SSRIs in the DM to examine this theory, and evaluate combining biomarkers from different conceptual models to achieve clinical synergy.

This study had several limitations that merit comment. First, it was not designed to have adequate statistical power to evaluate a relationship between the ESC-based biomarker and outcome with our BUP comparator, though such a relationship was found in prior work (Leuchter et al., 2009b). While a biomarker that predicts poor outcome for a given treatment at one week is useful, as it provides actionable information to change medication, it would be advantageous if it could suggest a successful alternative. Even in the absence of an affirmative prediction about response to BUP based on ATR, it is worthwhile to consider that ATR- subjects might be usefully switched from ESC, where they face a 30% likelihood of remission, to treatment with BUP where the odds are improved to 52.7%. As noted above, it is unknown whether an ATR- value with ESC predicts poor outcomes with all or most SSRIs, or only with ESC. This may be particularly germane given that remission probabilities with switching from one SSRI to another were not statistically different from those with switching "out of class" after an SSRI failure in Level 2 of the STAR*D trial (cf Gaynes et al., 2012). Future investigations could explore a wider range of test- and treatment-medication pairings to map out these relationships.

Second, because there was no placebo group, it is not possible to estimate the contributions of a specific medication response vs. a nonspecific, placebo-like response. In the EMBARC trial, baseline theta EEG activity in the anterior cingulate was a nonspecific prognostic marker of treatment outcome for both placebo and medication subjects (Pizzagalli et al., 2018). In contrast, in the only published study of the ATR index in a placebo-controlled trial context (Hunter et al., 2011), ATR was not related to clinical outcome in subjects receiving placebo but was for those subjects receiving fluoxetine. Given that placebo-mediated outcomes are thought to be short-lived compared with medication-driven effects, future studies could be designed to follow subjects into extended follow-up, to determine which remissions are sustained (cf Cook et al., 2013).

Third, it is useful to note that assessing clinical improvement with rating scales is already a part of the best practices of measurement-based care for depression (cf. Gelenberg et al., 2010; Lam et al., 2016), so recording qEEG data to determine ATR would be an additional step, though one which was well accepted in this project. Analyses of the utility of adding the ATR measure would depend upon the burden and costs of adding an EEG vs the benefits of moving patients to an effective treatment earlier; such cost-effectiveness modeling could also be undertaken as future work, as it is beyond the scope of this report.

Finally, this study was conducted at a single site with a modest sample size. A future multi-site trial design could confirm fidelity to implementation across clinics and expand the

sample size, and evaluate other factors, such as any gender-related differences in outcome, improving generalizability. As noted, there was a gender imbalance that our physiologically-based stratified randomization strategy did address, with the proportion of female subjects being higher in the ESC group than the BUP group. Such a larger study may also have adequate statistical power to explore the relationship between ATR and clinical improvement at intermediate time-points (e.g., speed of improvement).

In summary, the PRISE-MD study replicates and extends prior work with the ATR biomarker to help guide antidepressant selection in MDD. These results suggest that further development of this biomarker could lead to improved care by identifying which individuals should move on from a medication that is unlikely to be effective, and support that decision to change treatment after one week rather than after failing a full, multi-week course of medication.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

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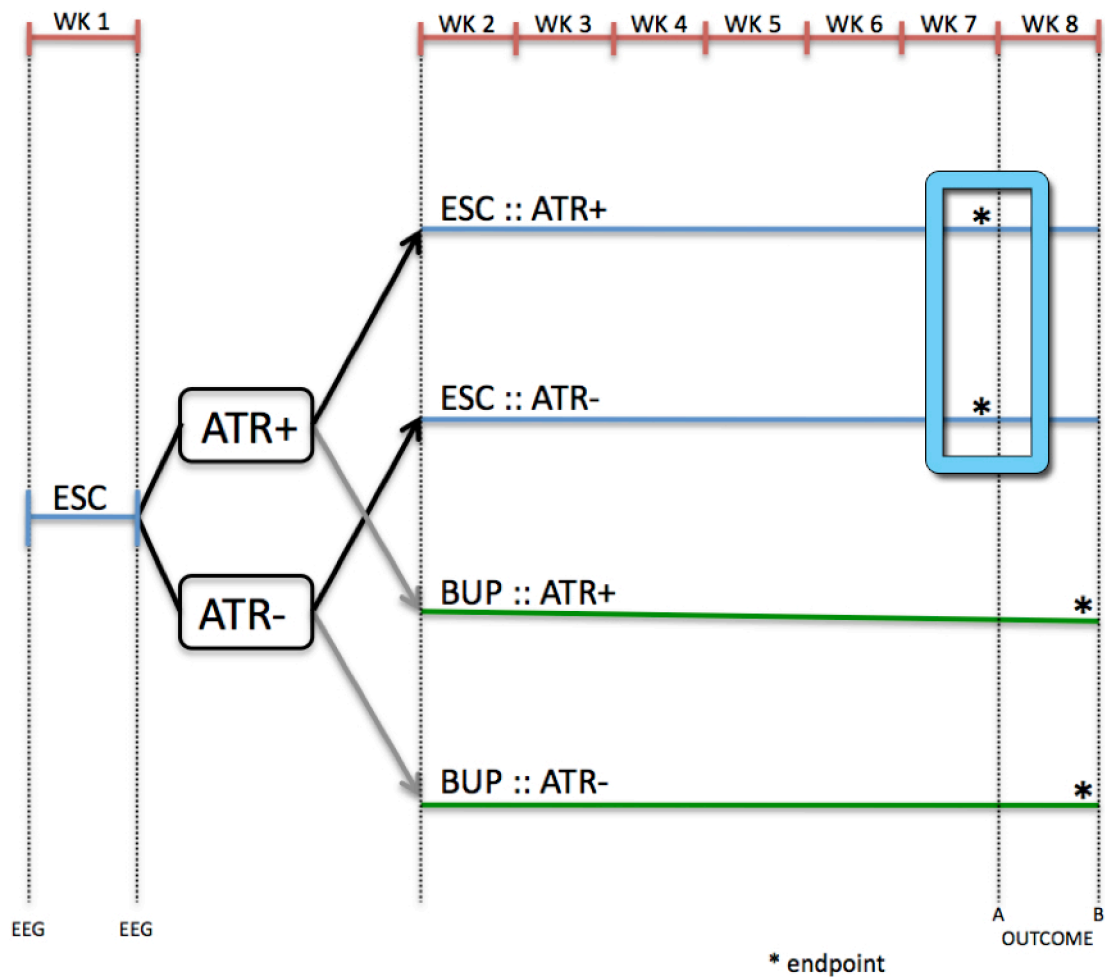
Figure 1. Study Design.
Based upon biomarker status (ATR+ or ATR−), subjects were assigned evenly to medication consistent or inconsistent with the biomarker prediction. Subjects used to evaluate primary hypotheses were assigned to escitalopram (ESC, blue lines within red box); other subjects were assigned to bupropion (BUP) in order to maintain blinding with clinical equipoise for our null hypothesis. Efficacy assessments were measured at weeks 7 and 8 (marked *) to maintain blinding.
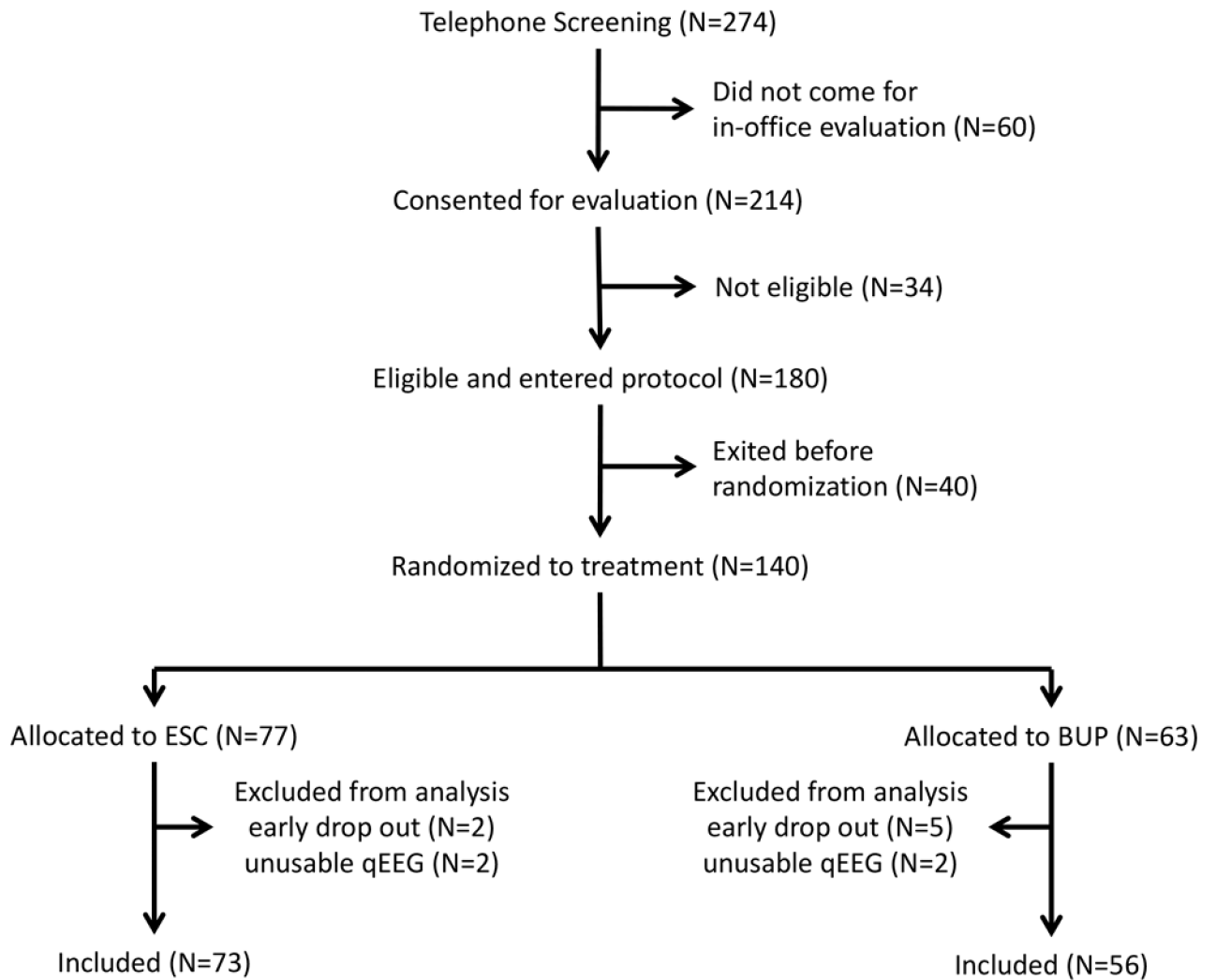
Figure 2. CONSORT diagram.
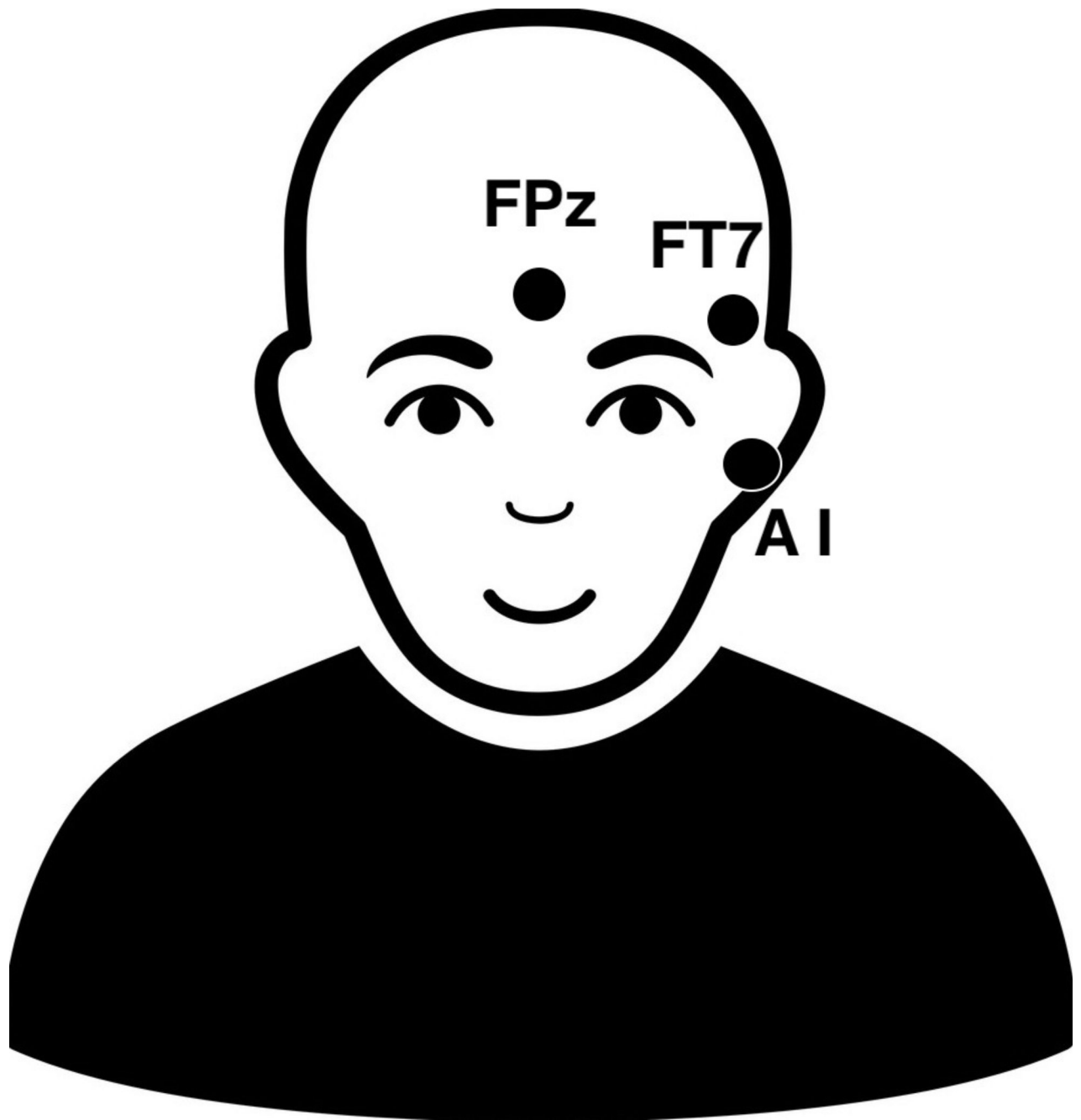73 individuals randomized to ESC form the basis for testing the primary hypotheses.

Figure 3. Electrode placement.
Midline (FPz) and left-sided (FT7, A1) electrode sites are shown; right-sided (FT8, A2) sites are placed at symmetric locations (not visible).
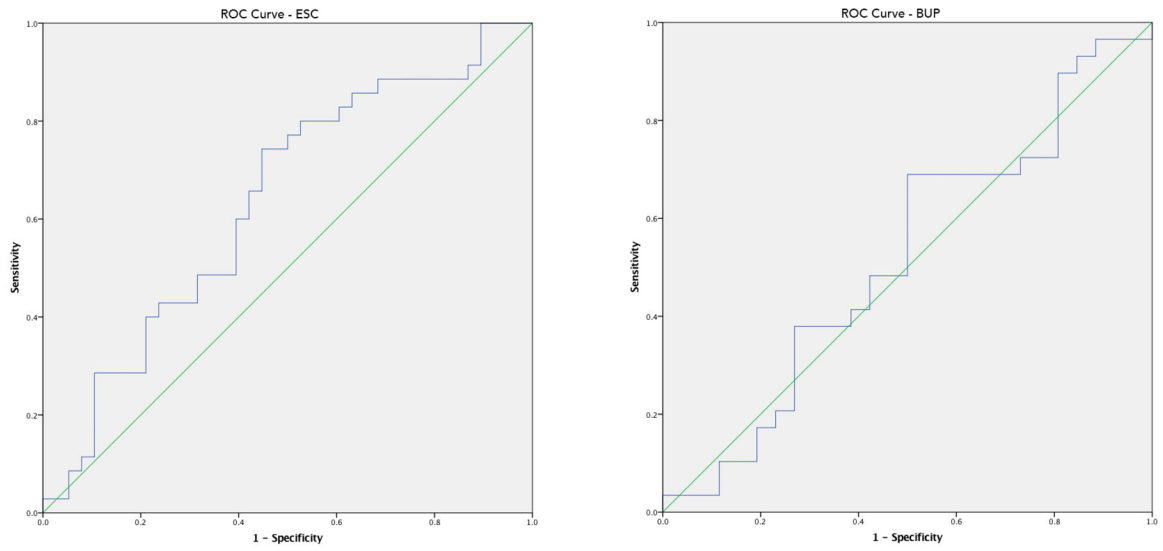
Figure 4. ROC Curves.
Curves show ATR as predictor of remission for ESC (left) and for BUP (right)