



Biomarkers for Rapid Identification of Treatment Effectiveness in Major Depression (BRITE-MD): Predictors of Clinical Response and Remission to Escitalopram Treatment

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ABSTRACT*

Background: The goal of this project was to evaluate early predictors of clinical response and remission to medication treatment in MDD.

Methods: Subjects meeting DSM-IV criteria for MDD began treatment with escitalopram (ESC; 10 mg/day) and were randomly assigned after 1 week to either: 1) continue ESC (10 mg/day); 2) augment with bupropion XL (AUG; 300 mg/day); or 3) switch to bupropion XL (BUP; 300 mg/day) for 7 weeks of treatment (www.BRITE-MD.org). Response was defined as a > 50% reduction in the 17-item Hamilton Depression Rating Scale (HAM-D-17) score from baseline to week 7. Remission was defined as a HAM-D-17 < 7 at week 7. Heart rate (HR), systolic (SBP) and diastolic (DBP) blood pressure, and 4-channel frontal quantitative electroencephalogram (fqEEG) were recorded at baseline. At week 1, plasma concentrations of ESC and desmethylscitalopram (dmESC) were assayed, depression severity using HAM-D-17 was assessed, and a second fqEEG was performed. In addition, clinicians were asked to predict the likelihood of response and remission based on global impression at one week. Blood samples for putative genetic biomarkers (for this report 5HT2a polymorphism) also were obtained. An EEG biomarker (Antidepressant Treatment Response [ATR] Index) developed to predict clinical response was tested using fqEEG at baseline and week 1. We hypothesized that ATR would be higher in responders and remitters than in non-responders and non-remitters. Student t and Chi-square tests as well as logistic regression were used as appropriate.

Results: 220 (78%) subjects (age: 43 ± 13; 62% female; 3% Asian, 14% Black, 19% Hispanic, 63% Caucasian) were evaluated after excluding protocol violators and subjects with excessive EEG artifact (ESC: n=73; BUP: n=73; AUG: n=74.) In the ESC arm of the study, 39 (52%) subjects responded and 28 (37%) subjects remitted. At one week, clinician global impression scores did not predict response or remission, but responders and remitters had significantly higher ATR (p<0.05) and significantly greater reduction in HAM-D (p < 0.05) compared to non-responders. Age, gender, race, HR, SBP, DBP, baseline HAM-D, and plasma levels of ESC + dmESC did not predict response or remission. 5HT2a polymorphisms had no association with response or remission. Logistic regression showed that ATR was the single best predictor of remission.

Conclusions: fqEEG and symptomatic changes at one week of treatment with ESC predicted clinical response and remission to ESC at seven weeks. Future studies are needed to evaluate the utility of these predictors in helping to guide antidepressant treatment decisions.

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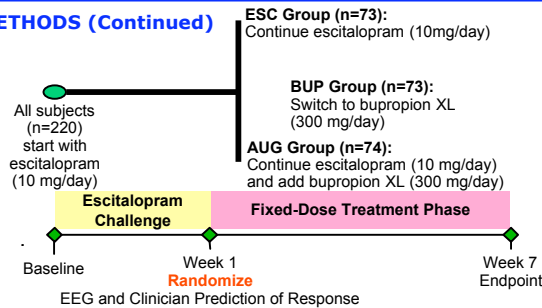
INTRODUCTION

- Prior work demonstrated that a simple-to-use frontal quantitative EEG (fqEEG) biomarker (Antidepressant Treatment Response (ATR) Index) predicted response to antidepressant treatment in MDD [1][2]
- This work prospectively evaluated the performance of ATR in predicting clinical response to escitalopram (ESC) versus bupropion (BUP) treatment

METHODS

- MDD subjects (DSM-IV criteria; baseline QIDS-SR ≥ 12) began treatment with with escitalopram (ESC; 10 mg/day) and were randomly assigned after 1 week to either: 1) continue ESC (10 mg/day); 2) switch to bupropion XL (BUP; 300 mg/day); or 3) augment with bupropion XL (AUG; 300 mg/day); for 7 weeks.
- Response was defined as a ≥ 50% reduction in HAM-D-17 from baseline to week 7 and remission as HAM-D-17 ≤ 7 at week 7

METHODS (Continued)



- At baseline, HAM-D-17, heart rate (HR), systolic (SBP), diastolic (DBP) blood pressure, and 4-channel EEG were recorded
- Blood was drawn to examine genetic biomarkers associated with treatment response. We report here on the association between response and the 5HT2a receptor polymorphism
- At week 1, plasma concentrations of ESC and desmethylscitalopram (dmESC) were assayed, clinician prediction of response based on global impression and the HAM-D-17 were assessed, and a second fqEEG was recorded
- ATR is a composite EEG index developed to predict clinical response (0 to 100, low to high likelihood) using fqEEG from baseline and week 1. ATR (version 4.0) was developed prior to BRITE. Interim BRITE data (i.e., first 111 patients) was used to refine ATR (version 4.1)

RESULTS

- 220 (78%) subjects were evaluated after excluding protocol violators and subjects with excessive EEG artifact (ESC: n=73, BUP: n=73; AUG: n=74)
- Of the 73 subjects treated with ESC:
 - 52% of subjects responded and 37% remitted.
 - Using a threshold to optimize accuracy, ATR (4.1) predicted response and remission each with 74% accuracy (p<0.001), performing better than the earlier version (4.0) which yielded accuracies of 60% (p=0.048) and 68% (p=0.012) for response and remission, respectively
 - Accuracy of clinician prediction of response and remission was not different from chance (p>0.05)
 - Percent reduction from baseline HAM-D was greater in responders than non-responders (37 ± 26 vs. 19 ± 25, p<0.001) and in remitters than non-remitters (37 ± 29 vs. 24 ± 25, p=0.016)
 - 5HT2a polymorphisms had no association with response or remission (p > 0.22)
 - Plasma levels of ESC + dmESC, age, race, gender, baseline HAM-D, HR, SBP and DBP did not predict response or remission
 - Logistic regression showed that the most accurate model for predicting remission utilized only ATR (p = 0.011)

RESULTS (Continued)

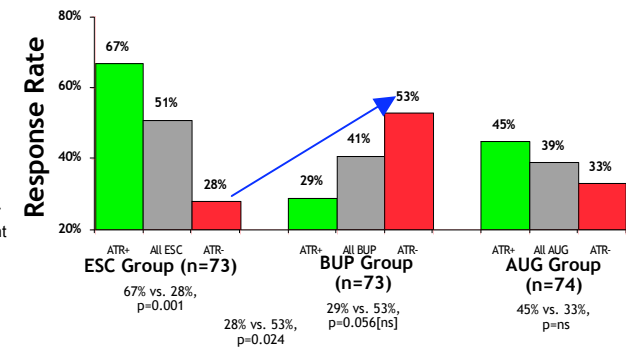


Figure 1. Response rates of subjects predicted by ATR (4.1) to respond to ESC treatment (ATR+, green), predicted by ATR not to respond to ESC (ATR-, red), or average response rate (grey) for each study limb.

- Because ATR-predicted non-responders to ESC treatment were more likely to respond to BUP therapy (see figure 1), ATR-guided treatment may improve overall response rates when redirecting ATR-predicted ESC non-responders to BUP treatment (28% vs. 53% response rate, p=0.024)
- Although percent reduction in HAM-D at 1 week predicted response to ESC, modeled use of this metric to switch subjects to alternate treatment did not significantly improve overall response rates

CONCLUSIONS

- ATR and percent change in HAM-D-17 after 1 week of escitalopram treatment predicted clinical response and remission at 7 weeks
 - Clinician prediction at 1 week was not better than chance
 - 5HT2a genotype had no significant association with response
- ATR may improve response rates when BUP is an optional alternate treatment. The utility of this predictor to help guide treatment decisions should be evaluated in future studies

REFERENCES

- [1] Iosifescu D, Greenwald S, Smith C, Devlin P, Alpert J, Hamill S, Fava M. **Frontal EEG at 1 Week Predicts Clinical Response to SSRI Treatment in Major Depressive Disorder**. Presented at the 2006 Annual Meeting of the American Psychiatric Association, Toronto, CA (#231).
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