The Establishing Moderators and Biosignatures Of Antidepressant Response for Clinical Care (EMBARC) Study: Rationale, Design and Progress

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Abstract

Background: Remission rates for Major Depressive Disorder (MDD) over 12 weeks of treatment are low (~30%) and unpredictable for any given antidepressant. Due to the clinical and biological heterogeneity of depression, it is unlikely that a single marker can have the specificity to guide treatment selection; 'biosignatures' composed of a set of markers are needed. These may be either: (1) moderators that optimize initial treatment choice or (2) surrogate endpoints (mediators) that can identify treatment outcome prospectively. The Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care (EMBARC) study was designed to address the need for biosignatures of treatment outcome and will advance personalized care of MDD. The study links a range of imaging, electrophysiological, and blood markers and behavioral/cognitive tasks to treatment response. These markers are validated additionally by the inclusion of a healthy control sample, assessed twice over one week which also provides test-retest reliability of early marker measurements in the clinical sample, and comparability across the four clinical sites of the study. The primary outcome of EMBARC will be a biosignature called the Depression Treatment Response Index (DTRI) which will integrate the biomarkers assessed into a single score that can be used to predict treatment outcome.

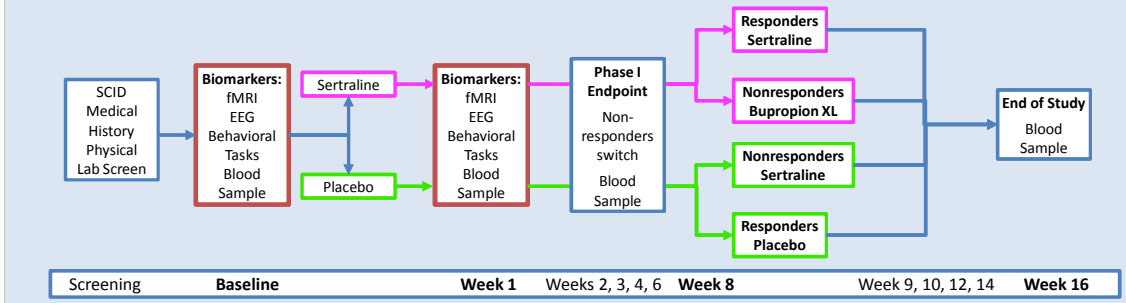
Methods: EMBARC has a two phase, randomized, placebo-controlled design. Adults, 18–65 with a diagnosis of MDD of at least moderate severity, and onset not later than age 35, are recruited while not taking any psychotropic medications. Baseline assessments are: (1) a comprehensive clinical phenotype including Structured Clinical Interview for DSM-IV (SCID); (2) imaging: anatomical magnetic resonance imaging, diffusion tensor imaging of white matter tracts, and functional MRI during an emotional conflict and a reward-dependent learning task, and pulsed arterial spin labeling; (3) quantitative electroencephalography (qEEG) to assess cortical and subcortical brain activation patterns and cortical evoked EEG potentials; (4) behavioral neuropsychological tasks assessing variables such as reaction time and motor processing speed and (5) blood marker collection including DNA, RNA, and plasma. Subjects are then randomized 1 : 1 to placebo or sertraline. After one week of treatment baseline assessments (with the exception of SCID and other diagnostic phenotyping) are repeated. Subjects then complete 8 weeks of treatment. At week 8, non-responder subject are switched in a blinded fashion to a second phase treatment (placebo right arrow sertraline, or sertraline right arrow bupropion XL) and responders continue taking their initial treatment. Blood markers are collected again at weeks 8, (9 in those who switch) and 16 and plasma level of medication is collected at weeks 1, 4, 8, 12 and 16 to control for medication adherence. Healthy subjects complete the baseline and week 1 assessments, but do not continue into treatment. Each marker will be analyzed for prediction of outcome both for the baseline assessment and the change between baseline and week 1. Markers showing predictive ability of outcome, including tolerance to medications will be integrated into the DTRI.

Results: As of mid-august 2013, 123 of 400 planned subjects have been randomized into the EMBARC trial. The healthy control sample has been completed at 52 subjects. Each biomarker category has had ongoing quality control procedures. We have completed test-retest reliability analyses on the healthy control cohort and applied them to the baseline data for the initial cohort of depressed subjects to control for across site differences. We are beginning analyze the first 100 subjects as compared to healthy controls as preliminary results of the study.

Conclusions: EMBARC advances the analysis of biomarkers for personalized care of depression by integrating a range of markers with excellent quality control in a well phenotyped sample with a placebo control. Results of the reliability assessments indicate that the use of rigorous quality control procedures across sites allows for larger multi-site trials to use complex procedures to assess the biological and psychological underpinnings of treatment response. This study is a first step in the development of biosignatures of treatment, and may also advance the understanding of the neurobiology of depression. The data will become available to the scientific community in a repository for further analyses to generate new findings.

Keywords: biomarkers, depression, neuroimaging, qEEG, antidepressants.

EMBARC Study Design



Innovation:

- Collect full range of biomarkers from a Healthy Control sample;
- Collect broad range of biomarkers in a randomized, placebo-controlled trial;
- Identify moderator and mediator markers from 2/3 sample and validate on remaining 1/3.

Specific Aims:

- Identify baseline clinical, neuroimaging, electrophysiological, and behavioral moderators of differential treatment outcome (mean symptom change and tolerability) for SERT vs. PBO
- Identify early phase (week 1) changes in neuroimaging, electrophysiological, and behavioral tasks as mediators of differential treatment outcomes (symptom change, tolerability)
- **Develop a depression differential treatment response index (DTRI) that integrates moderators across clinical and biological variables**

Table 1. Clinical Cohort: Current enrollment of depressed subjects, collected primary biomarkers, and study completion rates by site. Data reflects EMBARC status as of 12/1/13.

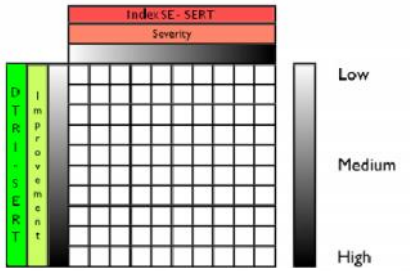
	Columbia University	Massachusetts General	University of Michigan	UT Southwestern	Total
Consented	45	103	66	112	326
Randomized	**35**	**21**	**34**	**67**	**157**
Baseline measures					
fMRI	35	21	34	66	156
EEG	35	21	34	67	157
Behavioral	35	21	34	67	157
Blood	35	21	34	67	157
Week 1 measures					
fMRI	31	16	31	60	138
EEG	33	15	29	61	138
Behavioral	33	15	29	61	138
Blood	32	16	30	61	139
Completed Stage 1	30	12	21	48	111
Completed Stage 2	23	8	13	36	80

Table 2. Complete enrollment, biomarkers and study completion rate for the Healthy Control comparison sample. *Three traveling subjects repeated all assessments at one other site.

	Columbia University	Massachusetts General	University of Michigan	UT Southwestern	Total
Consented	16	22	13	23	74
Randomized	12	15	12	13	52
Baseline/Week 1 measures*					
MRI	12/12	15/14	12/12	13/13	52/51
EEG	12/12	15/14	12/12	13/13	52/51
BePhe	12/12	15/15	12/12	13/13	52/52
Blood	12/11	15/15	12/12	13/13	52/51
Completed	12	14	12	13	51

Results and Conclusions: Enrollment in this multi-site comprehensive biomarker study has been accompanied by extensive quality control measures both at start-up of the project (including a feasibility sample) and through ongoing feedback from each of the data leads. The Healthy Control Cohort has been completed at all four sites: 10 additional subjects/site completed all biomarkers at Baseline and Week 1 and three of those subjects from each site also repeated the measures after traveling to one other site ("Week 2"). Analyses so far have focused on the completed Healthy Control Cohort. Test-retest reliability analyses have been completed for Imaging data, specifically, the reward task (poster #M059) and arterial spin labeling (poster #M072), and the EEG (poster #T155) and Behavioral Phenotyping data sets (poster #T151). Initial comparisons between depressed and healthy subjects are also presented for reward and ASL data (#M056 and #M065, respectively).

Figure 2. Schema for the EMBARC DTRI. Biomarkers predictive of symptom improvement and side effects will be integrated into a single score that indicates the probability of successful treatment.



DTRI = Depression Treatment response Index
SE = Side Effects

Improvement
1. Probability of response or remission on drug, or
2. Ratio of Probability of response or remission for Drug vs. Pbo, or
3. Change in depression severity from baseline to post-treatment, or
4. Ratio of change in depression severity from baseline to post-treatment for Drug vs. Pbo

Severity
1. SAFTE, or
2. FEBSER

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