

Referenced-EEG (rEEG) Efficacy Compared To STAR*D For Patients With Depression Treatment Failure:

First Look At Final Results

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BACKGROUND

Referenced-EEG (rEEG®) is a novel tool that provides medication guidance from a set of empirically derived biomarkers based on a quantitative electroencephalogram (QEEG). rEEG may have a role in guiding treatment for depressed patients. Several trials have investigated the use of rEEG efficacy in guiding Treatment Resistant patients with promising results. These studies were hampered, however, by their small sample sizes. A pilot study of rEEG (1), initiated in 2006, used the Texas Medication Algorithm Project (TMAP) algorithm as the control. Due to design problems the study blinding was compromised and the trial was stopped. A new design was developed using a modified medication algorithm based on the acute and long-term outcomes from the NIMH Sequenced Treatment Alternatives to Relieve Depression trial (STAR*D) (2). This standard was chosen because of its value in identifying the most effective antidepressants for treatment resistant patients.

OBJECTIVE

This study was designed to evaluate the efficacy of rEEG-based pharmacotherapy in comparison to medications guided by a leading standard (STAR*D) in the treatment of patients with depression treatment failure.

METHODS

This was a randomized, controlled, single-blind, parallel group, multicenter study, of rEEG-guided medication recommendations versus the most successful treatment regimens from the STAR*D study. Patients were recruited at twelve centers across the US, and from two basic strata: patients with depression treatment failure of one or more Selective Serotonin Reuptake Inhibitors (SSRIs), and those with failure of at least two classes of antidepressants. Subjects were 18 years or older with Major Depressive Disorder (MDD). Subjects were required to have a Quick Inventory of Depressive Symptomatology-Self Report-16 (QIDS-16-SR) of ≥ 13 and a Montgomery-Asberg Depression Rating Scale (MADRS) score of ≥ 6 at baseline. Potential subjects were excluded for medically relevant conditions, substance abuse, pregnancy or intent to become pregnant, lactation, or acute or chronic pain requiring prescription pain medication. All subjects underwent a washout of all current medications (except insulin, thyroxin, oral contraceptives, and hydrochlorothiazide) for a minimum of five half-lives prior to receiving a QEEG. The QEEG was analyzed utilizing rEEG technology. After the EEG, subjects were also excluded for reasons related to the EEG such as potential physiologic abnormalities or low abnormality in comparison to the current rEEG database. Also, subjects were excluded if the rEEG-guided treatment regimen would have been the same as the treatment regimen that the subject would receive if randomized to the control group. Subjects randomized to the rEEG group were assigned the

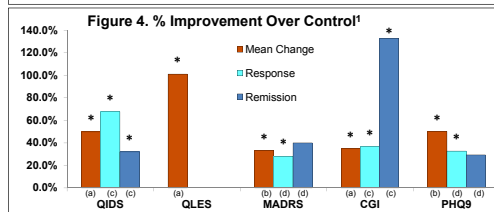
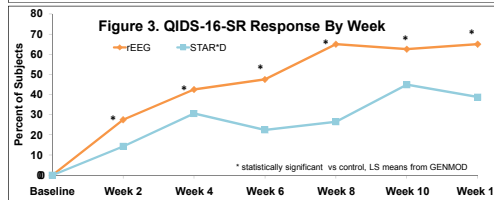
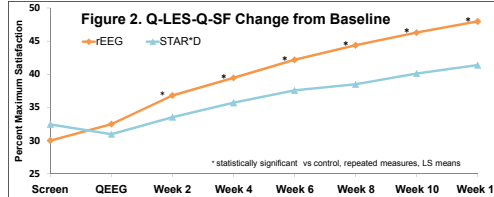
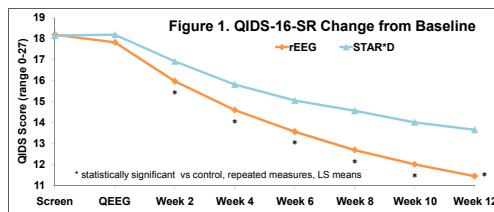
METHODS, continued

treatment regimen that was based on the rEEG report. Subjects randomized to the control group were assigned a treatment regimen based upon the STAR*D algorithm. Control subjects who had failed SSRI's only were treated with a venlafaxine XR; and subjects who had failed on medications from two or more classes of antidepressants were assigned a treatment regimen starting with Step 2 of the modified STAR*D algorithm. The treatment period was 12 weeks with site visits at Week 1, 2, 4, 6, 8, 10, 12. The primary and secondary outcome measures are listed in Table 1. Safety was assessed through collection of vital signs and adverse events (AEs) at each visit.

RESULTS

Demography: A total of 465 subjects were screened and 114 subjects were randomized (57 rEEG, 57 STAR*D). Of these, 44 were from the SSRI-only stratum, and 70 were from the stratum that failed two or more antidepressants. This population was on average 44 years old, 180 pounds, 63.2% female, 65.8% Caucasian, 15.8% Hispanic, and 9.6% Black. A total of 32 of the 114 randomized subjects (16 per group) prematurely terminated for: AEs (4), lack of efficacy (13), withdrawal consent (6), never took medications (3), and other reasons (6). The Modified Intent-to-Treat (MITT) population consisted of 104 subjects who were randomized and delivered valid data for the primary endpoints. The Per-Protocol (PP) population consisted of 89 MITT subjects who completed at least 2 weeks of treatment and fulfilled protocol criteria. Out of the 89 PP subjects analyzed for efficacy, 40 subjects were in the rEEG group and 49 subjects were in the STAR*D group (Table 1).

Efficacy Results: The primary endpoints (mean change from baseline for QIDS-16-SR and Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF) were both statistically significant (one-tailed, $\alpha = 0.05$) in favor of the rEEG treatment group (Table 1, Figures 1 and 2). QIDS-16-SR scores were reduced by a mean of 6.77 points vs 4.51 points, for rEEG vs STAR*D, respectively. Q-LES-Q-SF % Maximum Satisfaction increased by a mean of 18 percentage points vs only 8.95 percentage points, for rEEG vs STAR*D, respectively. The following secondary endpoints (Table 1) were also statistically significant in favor of the rEEG treatment group: QIDS-16-SR response (reduction by 50%) (Figure 3) and remission (score of 5 or less); MADRS mean change and response; Clinical Global Impression of Improvement (CGI-I) of either a 2 or 1 (much improved or very much improved) as well as those ONLY reaching 1; Patient Health Questionnaire (PHQ-9) mean change and response; and CGI-S mean change. A summary of rEEG improvement over STAR*D is shown in Figure 4. Although the protocol was designed for a one-tailed analysis, a two-tailed analysis ($\alpha=0.025$) of the primary endpoints was still statistically significant and 9 out of 12 secondary endpoints (Table 1) also met statistical significance.



* Statistically significant vs control.
 (b) per protocol population, CGI 'Response' bar is CGI of 2 or 1, CGI 'Remission' bar is CGI of 1.
 (c) Repeated measures, LS means/mixed procedure, (d) LS means from ANCOVA, (e) LS means from GENMOD, (f) Logistic analysis.

Table 1. Efficacy Results (Per Protocol Population)	rEEG N=40	STAR*D N=49	p-value
Primary Measures			
QIDS-16-SR mean change (a)	-6.77	-4.51	<.0001
Q-LES-Q-SF mean change (a)	18.0	8.95	<.0001
Secondary Measures			
QIDS-16-SR response (c)	65.00%	38.78%	<.0001
QIDS-16-SR remission (c)	35.00%	26.53%	0.0077
MADRS mean change (b)	-21.85	-16.43	0.0383
MADRS response (d)	57.50%	44.90%	0.0228
MADRS remission (d)	40.00%	28.57%	0.0335
CGI-I mean change (a)	-1.75	-1.30	<.0001
CGI-I scores of 2 or 1 (e)	72.5%	53.06%	<.0001
CGI-I scores of 1 (e)	47.5%	20.41%	0.0008
PHQ-9 mean change (b)	-13.73	-9.40	0.062
PHQ-9 response (d)	65.00%	48.98%	0.0055
PHQ-9 remission (d)	47.50%	36.73%	0.0645
CGI-Severity mean change (b)	-2.32	-1.46	0.0007

(a) Repeated measures, LS means/mixed procedure. (b) LS means from ANCOVA. (c) LS means from GENMOD. (d) Logistic analysis.

CONCLUSIONS

This study demonstrated that rEEG-guided pharmacotherapy was highly effective in the treatment of subjects with depression treatment failure. rEEG efficacy was compared to STAR*D and demonstrated statistically significant superiority on nearly every parameter measured (QIDS-16-SR, QLESQ, MADRS, CGI, CGS and PHQ-9). This suggests that rEEG should be considered as a useful tool in the selection of medications for this difficult-to-treat population. These results warrant additional studies in the role of rEEG-guided psychopharmacology for this non-psychotic depressed psychiatric population.

REFERENCES

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INFORMATION

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