Fall 11-21-2021

Clinical Predictors of Response to Depression Treatment in Persons with Epilepsy

Juliana Hager
The University of Texas Rio Grande Valley, juliana.hager01@utrgv.edu

Frank Gilliam
The University of Texas Rio Grande Valley, frank.gilliam@utrgv.edu

Clinical Predictors of Response to Depression Treatment in Persons with Epilepsy

Juliana Hager, Frank G. Gilliam, MD, MPH

Abstract:

Background

The literature on predictors of response to treatment of depression for persons with epilepsy is limited. This study examined predictors of response to treatment of major depression disorder (MDD) by cognitive behavioral therapy (CBT) or Sertraline in Epilepsy patients.

Methods:

In the original two-site comparative effectiveness trial, 140 adult outpatients with active epilepsy and current major depressive disorder were randomly assigned to either sertraline (at a dose starting at 50 mg per day, titrating as needed at two-week intervals up to 200 mg per day) or weekly cognitive behavior therapy (CBT) for 16 weeks[1]. The primary outcome measure was the depression module of the MINI-International Neuropsychiatric Interview (M.I.N.I.). Secondary outcomes included the Quality of Life in Epilepsy Inventory (QOLIE)-89, seizure rates, the Adverse Events Profile (AEP), the Beck Depression Inventory II, and the M.I.N.I. Suicide Risk Module. A logistic regression model analysis was performed on patient clinical, psychosocial, and demographic variables previously identified as significantly significant in an attempt to develop a predictive model for positive MDD treatment response in persons with Epilepsy.

Results:

The variable that was predictive of MDD treatment response was the severity of the depression at baseline according to the Centers for Epidemiological Studies- Depression (CES-D) with a more severe baseline depression showing a lower response rate.

Conclusion:

The more severe MDD at baseline in epilepsy patients was shown to be predictive of a lower response to depression treatment with Sertraline or CBT in persons with Epilepsy.

Introduction:

The clinical usefulness of predictors of response to treatment is obvious. Several studies have investigated the clinical predictors of response to acute treatment of major depressive disorder[2]. There is no literature on the predictors of response to MDD treatment in persons with Epilepsy. Epilepsy affects over 1% of the US population[3]. Depression is the most common comorbid disorder in epilepsy, and is associated with reduced quality of life, increased health-care utilization, and greater mortality[4-7]. A recent population-based study found that suicide is increased 32-fold in persons with a history of both epilepsy and affective disorder compared to the general population [8].

A randomized control trial of Sertraline and Cognitive Behavioral Therapy was done for persons with Epilepsy and MDD. Depression improved following sertraline or CBT, with most subjects in both groups achieving remission. Despite the complex psychosocial disability associated with recurrent seizures, improving depression can have a substantial benefit to quality of life. This study examines predictors of response to depression treatment with persons with epilepsy. The data comes from the RCT trial of Sertraline and CBT for depression in Epilepsy, two-site comparative effectiveness trial[1].

Material and Methods:

In the original study, a 16-week intervention intended to eliminate depression was administered. The study randomly assigned 140 adult outpatients with epilepsy and current major depressive

disorder to sertraline or weekly CBT for 16 weeks. Each subject's physician continued epilepsy management. Either sertraline or CBT was the treatment for depression. Sertraline was initiated at 50mg per day and increased by 50mg at 2-week intervals as needed for a CES-D score > 14, up to a maximum dose of 200 mg per day. Cognitive behavior therapy was administered by a licensed therapist using standardized, manual-based Beck guidelines in a 1-hour session each week. The therapist completed a weekly written assessment to document the components of CBT utilized in each session. Participants were encouraged to attend every session in person, but a minority of the sessions could be performed by telephone in consideration of transportation limitations of many persons with epilepsy. If subjects stopped assigned treatment but did not withdraw consent to participate, the protocol allowed outcomes assessments to be continued for the entire 16-week study period.

Baseline assessments were made prior to randomization. Subjects were re-evaluated with each outcome measure during a research clinic visit every 4 weeks. A telephone assessment for depression severity (Beck Depression Inventory [BDI] and CES-D), seizures, and treatment side effects was obtained at the 2-week interval between clinic visits. A detailed description of the rationale and design of the overall project may be found in *Gilliam FG et al*[1].

The statistical analysis of the data was carried out with the statistical package SPSS Version 27 in two steps. Variables were selected for inclusion of the analysis based on their known association with depression and were assessed at baseline. These included gender, age, years of education, baseline depression severity scores (CES-D), baseline QILIE-89 score, experiencing a generalized tonic-clonic seizure ever, ethnicity, driving status, marital status, employment status, epilepsy foundation of America Concerns Index (EFA) score, and the social support and social isolation subscale scores measured on the QOLIE-89 at baseline.

First, any possible association between each independent variable was explored in univariate analysis; for two quantitative variables a chi-squared test was used, while a t-test for differences between means was used for continuous variables. Finally, to estimate the effect of each independent variable on the depression remission, logistic regression models were run. The dichotomous variable in the logistic regression model is MDD active or in remission at sixteen weeks (based on the MINI score). All the hypotheses were rejected at an alpha level of .05.

Results:

A total of 140 participants were enrolled and randomly assigned to either the sertraline or CBT treatment groups. At enrollment the mean age of the cohort was 39 years, seventy-seven subjects were women. No differences were found between treatment groups with respect to baseline number of seizure medications, BDI scores, CES-D scores, AEP scores, or QOLIE-89 scores. As a comparative effectiveness trial, the protocol allowed follow up after stopping assigned treatment, so that 117 (83.6%) participants completed assessments at week 16.

Of the 117 subjects that completed the final assessment, the mean BDI scores at baseline and week 16 for the sertraline group (n=59) were 24.2 (s.d 8.4) and 12.3 (s.d. 9.9), and for the CBT group (n=58) were 26.9 (s.d. 10.5) and 12.8 (s.d. 11.9). Of the 96 subjects that completed the MINI at week 16, 38 of the 48 (79.2%; 95%CI±11.5) in the sertraline group and 41 of 48 (85.4%; 95% CI±10.0) in the CBT group were in remission from major depression (between

group chi-square=0.64; p =0.42).For a detailed description of the original patient group, see the original study (Guilliam FG).
The the primary univariate analysis showed that the baseline CES-D (p-value< .0001), and ethnicity (p-value<.00001) were statistically significant variables (Tables 1&2)

We included in the logistic regression the variables that were found to be statistically significant on univariate analysis. The logistic regression model showed that the baseline severity of depression based on the CES-D score was a significant clinical predictor of response to depression treatment in Epilepsy persons (p< .035 with a OR 1.062) (Table 3). The more severe the MDD was at baseline, the higher the CES-D, the less likely the patient with Epilepsy was to respond to depression treatment.

Table 1: Relationship of continuous variables at baseline and MDD Remission based on the MINI score at 16 weeks

	Depression Remission at 16 Weeks	Depression Active at 16 Weeks	*P*
Education Years (Mean)	14.37	13.96	0.50
Age (Mean)	40.68	37.08	0.17
CES-D (Mean)	29.09	36.71	**0.00***
QOLIE-89 (Mean)	56.12	57.71	0.70
EFA (Mean)	58.70	66.21	0.07

Table 2: Relationship of qualitative variables at baseline and MDD Remission based on MINI score of 16 weeks

	Depression Remission at 16 Weeks	Depression Active at 16 Weeks	*P*
Gender			0.53
Female	52	12	
Male	39	12	
Ethnicity			**0.00***
Hispanic or Latino	0	4	
Not Hispanic or Latino	91	20	
Driving Status			0.99
Yes	38	10	
No	53	14	
Marital Status			0.35
Married	38	9	
Not Married	47	15	
Member of an unmarried couple	6	0	
Occupational Status			0.46
Employed	43	8	
Student	5	2	
Not Employed	43	14	
Social Support Subscale Score			0.29
.00	1	1	
6.25	1	0	
12.50	1	0	
18.75	5	0	
25.00	5	5	
31.25	5	1	
37.50	4	1	
43.75	12	6	
50.00	13	2	
56.25	11	0	
62.50	7	0	
68.75	3	2	
75.00	7	3	
81.25	5	1	
87.50	5	2	
93.75	2	0	
100.00	4	0	
Social Isolation Subscale Score			0.22
.00	3	3	
10.00	5	0	
20.00	12	5	
30.00	8	1	
40.00	13	6	
50.00	8	4	
60.00	13	3	
70.00	10	1	
80.00	9	0	
90.00	4	1	
100.00	6	0	
Generalized Tonic Clonic Seizure Ever			0.98
Yes	15	4	
No	76	20	

Table 3: Variables at baselines most related to MDD Remission based on the MINI Score at 16 Weeks

	β	SE	OR	*P*	Model *P*
CES-D (Mean)	0.61	0.03	1.062	0.035	<0.0001
Ethnicity	21.84	19779.265	0.000	0.999	<0.0001

Discussion:

In this study we aimed to evaluate the predictive variables to depression treatment that can be obtained in clinical evaluation of persons with Epilepsy. The ethnicity variable, while significant in the univariate analysis was not significant in the logistic regression. Only four of the patients were of Hispanic or Latino origin, so these results cannot be representative of the population. A more representative population of a Hispanic population should be further studied. A further analysis of variables in each treatment group (Sertraline vs CBT) could yield more specific data.

References

1. Gilliam, Frank G et al. "A Trial of Sertraline or Cognitive Behavior Therapy for Depression in Epilepsy." *Annals of neurology* 86.4 (2019): 552–560. Web.
2. Hirschfeld RM, Russell JM, Delgado PL, Fawcett J, Friedman RA, Harrison WM, Koran LM, Miller IW, Thase ME, Howland RH, Connolly MA, Miceli RJ. Predictors of response to acute treatment of chronic and double depression with sertraline or imipramine. J Clin Psychiatry. 1998 Dec;59(12):669-75. doi: 10.4088/jcp.v59n1205. PMID: 9921701.
3. Kobau R, Zahran H, Thurman DJ, Zack MM, Henry TR, Schachter SC, et al. Epilepsy surveillance among adults--19 States, Behavioral Risk Factor Surveillance System, 2005. Morbidity and mortality weekly report Surveillance summaries. 2008;57(6):1-20.
4. Fazel S, Wolf A, Langstrom N, Newton CR, Lichtenstein P. Premature mortality in epilepsy and the role of psychiatric comorbidity: a total population study. Lancet. 2013;382(9905):1646-54.
5. Boylan LS, Flint LA, Labovitz DL, Jackson SC, Starner K, Devinsky O. Depression but not seizure frequency predicts quality of life in treatment-resistant epilepsy. Neurology. 2004;62(2):258-61.
6. Cramer JA, Blum D, Fanning K, Reed M, Epilepsy Impact Project G. The impact of comorbid depression on health resource utilization in a community sample of people with epilepsy. Epilepsy Behav. 2004;5(3):337-42.
7. illiam F. Optimizing health outcomes in active epilepsy. Neurology. 2002;58(8 Suppl 5):S9-20.
8. Christensen J, Vestergaard M, Mortensen PB, Sidenius P, Agerbo E. Epilepsy and risk of suicide: a population-based case-control study. Lancet neurology. 2007;6(8):693-8.