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A Trial of Sertraline or Cognitive Behavior Therapy for Depression in Epilepsy

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Abstract

Objective: Limited evidence is available to guide treatment of depression for persons with epilepsy. We evaluated the comparative effectiveness of sertraline and cognitive behavior therapy (CBT) for depression, quality of life, seizures, and adverse treatment effects.

Methods: We randomly assigned 140 adult outpatients with epilepsy and current major depressive disorder to sertraline or weekly CBT for 16 weeks. The primary outcome was remission from depression based on the Mini International Neuropsychiatric Interview (MINI). Secondary outcomes included the Quality of Life in Epilepsy Inventory-89 (QOLIE-89) seizure rates, the Adverse Events Profile (AEP), the Beck Depression Inventory, and MINI Suicide Risk Module.

Results: In the intention-to-treat analysis, 38 (52.8%; 95% confidence interval [CI] = ± 12) of the 72 subjects assigned to sertraline and 41 (60.3%; 95% CI = ± 11.6) of the 68 subjects in the CBT group achieved remission; the lower bound of efficacy for both groups was greater than our historical placebo control group upper bound of 33.7%. Difference in time to remission between groups was 2.8 days (95% CI = ± 0.43 ; $p = 0.79$). The percent improvement of mean QOLIE-89 scores was significant for both the CBT (25.7%; $p < 0.001$) and sertraline (28.3%; $p < 0.001$) groups. The difference in occurrence of generalized tonic-clonic seizures between groups was 0.3% (95% CI = ± 8.6 ; $p = 0.95$). Suicide risk at final assessment was associated with persistent depression ($p < 0.0001$) but not seizures or sertraline.

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Author Contributions

F.G.G., P.J.L., K.E.F., and Y.I.S. contributed to the conception and design of the study. F.G.G., K.B., K.E.F., J.C., and W.-Y.T. contributed to the acquisition and analysis of the data. F.G.G., K.B., K.E.F., J.C., Y.I.S., and W.-Y.T. contributed to drafting the text and preparing the figures.

Potential Conflicts of Interest

Nothing to report.

Interpretation: Depression remitted in just over one-half of subjects following sertraline or CBT. Despite the complex psychosocial disability associated with epilepsy, improving depression benefits quality of life. Serotonin reuptake inhibition does not appear to increase seizures or suicidality in persons with epilepsy.

Epilepsy is a chronic, potentially disabling disorder that affects over 1% of the world population.^{1,2} Depression is one of the most common comorbid disorders in epilepsy, and is associated with reduced quality of life and medication adherence, increased health care utilization, and premature mortality.^{3–7} Epidemiological data indicate that over 1 million people in the United States have suffered from the combination of both epilepsy and depression within the past year.⁸ A 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.⁹ Another large study of premature mortality in epilepsy concluded that “of those who died from external causes, 75.2% had comorbid psychiatric disorders, with strong associations in individuals with co-occurring depression (13.0, 10.3-16.6).”³

The optimal approach to the treatment of depression associated with epilepsy is unclear, with limited evidence supporting efficacy of antidepressant therapies.^{10–13} Despite methodological limitations, some studies suggest that antidepressants can cause or worsen seizures,¹⁴ and the US Food and Drug Administration (FDA) labeling information for most selective serotonin reuptake inhibitors (SSRIs) recommends caution in persons with a history of seizures.¹⁵ Additional concerns arise from FDA warnings regarding the potential induction of suicidal thoughts and behaviors with either antidepressant or antiepileptic medications. Antidepressants as a class are the leading cause of adverse medication effects in ambulatory care,¹⁶ which could exacerbate the adverse effects from antiseizure medications that are a prominent influence on quality of life in persons with epilepsy.^{17–19}

We performed a randomized trial designed to compare depression and multiple secondary health outcomes of sertraline and cognitive behavior therapy (CBT) in persons with current major depression and active epilepsy ([ClinicalTrials.gov](https://clinicaltrials.gov) identifier,). Depression severity, seizure occurrence, adverse treatment effects, quality of life, and suicidal risk were systematically assessed with reliable and valid measures.

Patients and Methods

Patient Sample and Inclusion and Exclusion Criteria

Subjects were recruited from the general neurology and subspecialty epilepsy clinics at Columbia University and Washington University, as well as through announcements in local periodicals. The institutional review boards at the respective institutions approved all recruitment documents, including fliers, announcements, and informed consent forms. Each patient signed an approved informed consent document prior to screening for significant symptoms of depression, and then another more detailed consent form if they met entry criteria. Subjects were offered enrollment if they met the following inclusion and exclusion criteria: (1) age between 21 and 75 years; (2) diagnosis of epilepsy confirmed by a board-certified neurologist with subspecialty training in epilepsy; (3) occurrence of an absence, focal with impaired awareness, or generalized motor seizure within the past 12 months while

taking a recommended dose of an approved antiseizure medication; (4) score of >14 on the Centers for Epidemiological Studies Depression Scale (CES-D); (5) diagnosis of current major depressive episode on the Mini International Neuropsychiatric Interview (MINI), and (6) able to read and understand study documents based on investigators' assessment. Exclusion criteria included (1) suicide attempt within the past year, (2) current alcohol or other substance abuse disorder, (3) history of bipolar depression or psychotic disorder, (4) pregnant or lactating, (5) prior hypersensitivity reaction to sertraline, (6) progressive central nervous system disorder (such as tumor or multiple sclerosis), or (7) significant medical illness such as hepatic or renal disorder (serum creatinine >3mg/dl).

Randomization

Participants were assigned in equal proportion to either treatment group by a simple, nonstratified electronic randomization procedure. The randomization code was generated by a computer program by a noninvestigator at Washington University. The code was kept in a locked computer in a secure room. Only a single study administrator had access to the code, which was masked prior to assignment. Treatment assignment for Columbia University participants was obtained by telephone communication.

Study Management and Procedures

Research assistants who were aware of the intervention implemented the study procedures. We did not attempt to blind research assistants collecting outcome data because we were unable to ensure blinding based on our pilot studies of CBT. The MINI was administered by a research coordinator trained in clinical use of the instrument and supervised by the principal site investigators. Baseline assessments were made prior to randomization. For any diagnostic uncertainty, an urgent psychiatric consultation was obtained for more definitive diagnosis prior to enrollment. If depression symptoms worsened during treatment or suicidal ideation occurred in the study, a psychiatry consultation was immediately obtained. If serum electrolytes, glucose, renal function tests, and hepatic function tests were not available from the past 6 months, or if recent medical history suggested current renal or hepatic dysfunction, serum testing was obtained at the initial visit. Following screening, enrollment, and baseline assessment, 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. All results were entered into an electronic database managed by the study statistician (W.-Y.T.). The study was overseen by a data and safety monitoring board (DSMB) designated by the National Institute of Neurologic Disorders and Stroke (NINDS). Site investigators (F.G.G. and K.J.B.) were blinded to outcome assessments, and did not have access to study documents or database prior to the completion of the trial and DSMB approval of the final outcome analysis. The protocol template, manual of procedures, and case report forms were designed in accordance with the NINDS Clinical Research Toolkit and Common Data Elements.²⁰

Treatment Program

A 16-week intervention intended to eliminate depression was administered. 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 200mg per day. Cognitive behavior therapy was administered by a licensed therapist using standardized, manual-based Beck guidelines in a 1-hour session each week.²¹ The therapist completed a weekly written assessment to document the components of CBT utilized in each session. If approved by the subject, CBT sessions were taped for quality monitoring (K.E.F). 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 (Fig 1).

Outcome Measures

Each of the outcome measures was selected based on results of prior reliability and validity testing, especially in epilepsy samples when available. The primary outcome was the proportion of participants achieving remission from depression based on the MINI.²² Secondary measures of depression severity included the BDI, with 21 questions, and the CES-D, with 20 items.²³ Suicide risk was determined by the suicide module of the MINI.²⁴ Quality of life was assessed by the 89-item Quality of Life in Epilepsy Inventory (QOLIE-89), for which a total score gives an estimate of overall health-related quality of life.^{6,25} Medication side effects were determined by the Adverse Events Profile (AEP), which has 19 items.^{18,19} Seizure rate and severity was assessed by standardized seizure calendars that coded each seizure based on the International League Against Epilepsy classification.²⁶

Statistical Analyses

The statistical plan was initially approved by the NINDS review section and subsequently by the DSMB. Two prior randomized, placebo-controlled trials of the treatment of depression in chronic medical illness from our group (P.J.L and K.E.F.) demonstrated a 50% remission rate with an SSRI or CBT and a 23% remission rate with a placebo^{27,28}; sample size calculation of this difference determined that 65 subjects in each treatment group provided a power of 0.81 to detect a significant difference at a 2-sided 0.05 significance level compared to our historical placebo controls. The 13 of 57 (22.8%) historical placebo controls that achieved remission allowed calculation of the upper bound of the remission rate for placebo (95% confidence interval [CI] = 11.9–33.7%). Descriptive data are presented as mean and standard deviation (SD), median and range, and percentage. A Kaplan–Meier curve was plotted with a log rank test of time in depression for each treatment group based on a BDI score > 12. χ^2 tests were used to compare categorical variables such as MINI classification of depression and suicide risk. The Student *t* test was used to compare continuous variables. Linear regression assessed association of change in QOLIE-89 score with change in seizure rate, BDI score, and AEP score. Logistic regression evaluated association of suicide risk on the final MINI with major depression status, treatment assignment, overall seizure rate in final month, and initiation of a new seizure medication during the study. Hypothesis testing utilized subjects who had not had a generalized tonic-clonic (GTC) seizure in the 6 months prior to enrollment, with 1-sided testing of the hypothesis that sertraline is associated with a

greater than 15% occurrence of GTC seizures compared to CBT. Missing data were assumed to be random so that multiple imputations could be used. For the intent to treat analysis, missing MINI results were imputed to be major depressive episode. Significance was determined by a $p < 0.05$ for all analyses.

Results

Study Participants

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 39.6 years. Seventy-seven subjects were women. One hundred twenty-seven (90.7%) of the subjects had not received prior treatment for depression. There were no differences among treatment groups, including within each site, with respect to demographic characteristics (Table 1). 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. Four subjects (5.6%) in the sertraline group and 5 (7.3%) in the CBT group stopped assigned treatment but continued assessments. In the sertraline group, 5 (6.9%) subjects crossed over to CBT. In the CBT group, 2 (2.9%) participant crossed over to sertraline therapy. Sensitivity analysis showed that the crossover of treatments by these 7 subjects did not affect the depression outcomes results. Six subjects in the CBT group and 9 in the sertraline group did not return to study visits and did not respond to telephone calls, and were subsequently classified as lost to follow-up. The subjects lost to follow-up did not differ between the sertraline and CBT groups in time to exit (7.2 vs 4.8 weeks; $p = 0.40$), or any demographic or clinical characteristic listed in Table 1. Mean time in the trial for the entire 140-subject cohort was similar for both treatment groups (sertraline 12.9 weeks, SD = 5.3; CBT 13.0 weeks, SD = 5.3; $p = 0.85$).

Depression and Suicidality Outcomes

The mean number of CBT sessions per patient was 12.1, with an average of 8.5 in person and 3.6 by telephone. The percentage of subjects taking each dosage level of sertraline was 18.4% for 50mg, 36.7% for 100mg, 24.5% for 150mg, and 20.4% for 200mg. In the intention-to-treat analysis, 38 (52.8%; 95% CI = ± 12) of the 72 subjects assigned sertraline and 41 (60.3%; 95% CI = ± 11.6) of the 68 in the CBT group achieved remission based on the MINI (between- group $\chi^2 = 0.80$; $p = 0.37$). The lower bound of the 95% CI of the proportion in remission for each treatment group was greater than the upper bound of the historical placebo-control group (33.7%). Of the 117 subjects who completed the final assessment, the mean BDI scores at baseline and week 16 for the sertraline group ($n = 59$) were 24.2 (SD = 8.4) and 12.3 (SD = 9.9), and for the CBT group ($n = 58$) the scores were 26.9 (SD = 10.5) and 12.8 (SD = 11.9). Each interval and final mean BDI score was significantly improved compared to baseline ($p < 0.005$; Table 2). Kaplan–Meier analysis curves for probability of continued depression based on BDI > 12 for sertraline and CBT groups found no significant difference (log-rank $\chi^2 = 0.07$; $p = 0.79$), as shown in Figure 2. The difference in time to remission between the groups was 2.8 days (95% CI = ± 0.43 days;

Table 3). Of the 96 subjects who completed the MINI at week 16, 38 of the 48 (79.2%; 95% CI = $\pm 11.5\%$) in the sertraline group and 41 of 48 (85.4%; 95% CI = $\pm 10.0\%$) in the CBT group were in remission from major depression (between-group $\chi^2 = 0.64$; $p = 0.42$). Logistic regression for the MINI suicide risk at week 16 showed a significant association of increased risk with current major depression ($\beta = 1.86$; $p < 0.0001$), but not seizure rate, treatment assignment, or initiation of a new antiepileptic drug during the study. Remission from depression was similar ($p = 0.81$) at week 16 between subjects with focal epilepsy (82.4%) and idiopathic generalized epilepsy (79.7%).

Quality-of-Life Outcomes

Mean QOLIE-89 total scores improved from 51.5 (SD = 14.9) in the screening visit to 66.1 (SD = 17.7) in the final visit for the sertraline group (28.3% improvement; $p < 0.001$), and from 50.1 (SD = 13.6) to 63.0 (SD = 18.4) in the CBT group (25.7% improvement; $p < 0.001$). No significant difference in QOLIE-89 total scores was found between groups at any interval assessments during the study (Fig 3). Linear regression analysis found that change in BDI and AEP scores ($p < 0.0001$ for both), but not change in seizure rate, were independently associated with change in QOLIE-89 scores.

Seizure Outcomes

The primary seizure outcome assessment, occurrence of a GTC seizure during the study in subjects who had not experienced a GTC in the 6 months prior to enrollment, was not significantly different between the sertraline (4/51; 7.8%) and CBT (4/53; 7.5%) groups ($p = 0.95$). This difference between GTC seizure occurrence of 0.3% (95% CI = -8.3 to 8.9%) allowed rejection of the null hypothesis ($p = 0.002$) that $>15\%$ more GTC seizures would occur in the sertraline group. The reduction in monthly GTC seizure rates from baseline in the sertraline group ($p < 0.005$ at week 8) further supports rejection of the null hypothesis (see Table 2). Focal impaired awareness seizures were the most common seizure type in the study, occurring in 45 subjects in the sertraline group and 38 subjects in the CBT group. The screening visit seizure rate was a retrospective estimate of the monthly average for the prior 3 months, and was not significantly different ($p = 0.26$) for focal unaware seizures between the sertraline (2.3; SD = 4.7) and the CBT (7.1; SD = 26.4) groups (see Table 2). This monthly average decreased to 0.8 (SD = 4.5) in the sertraline group and 3.8 (SD = 13.3) in the CBT group, but the change was not significant within or between groups at the final assessment. Achieving remission for depression on the MINI was associated with a significant decrease in mean monthly GTC seizure rate between baseline and week 16 for the whole study cohort (-0.07 , SD = 0.27 for remission group vs $+0.06$, SD = 0.24 for continued depression group; $p = 0.04$), but the difference was not significant within the treatment group for sertraline (-0.07 , SD = 0.29 vs $+0.09$, SD = 0.21; $p = 0.07$) or CBT (-0.06 , SD = 0.26 vs $+0.03$, SD = 0.28; $p = 0.31$). The mean monthly rate of focal impaired awareness seizures for the study cohort decreased by 0.48 (SD = 4.68) in the group that achieved depression remission, compared to an increase of 1.7 (SD = 7.66) in the group with continued depression ($p = 0.09$); similarly, the decrease was not significant for the sertraline group (-0.10 , SD = 3.42 vs $+0.15$, SD = 1.28; $p = 0.81$) or the CBT group (-0.88 , SD = 5.71 vs $+3.15$, SD = 10.78; $p = 0.08$).

Tolerability and Adverse Events

Ten serious adverse events occurred in the sertraline group, and 3 were considered possibly related to the study; these included a subject with mania and psychosis, and 2 subjects with worsening depression that required hospitalization. Twelve serious adverse events occurred in the CBT group, and 3 were possibly related to the study; these consisted of 3 subjects who developed worsening depression and suicidal ideation that required evaluation in an emergency department. One death occurred in the study, which was a subject in the CBT group who had presumed sudden unexpected death in epilepsy. Ten adverse effects occurring in >5% of subjects were reported in the CBT group, and 15 were reported in the sertraline group (Table 4). AEP scores decreased from a mean of 48.1 (SD = 8.1) at baseline to 39.0 (SD = 11.4) at week 16 for the sertraline group, and 47.4 (SD = 7.9) to 41.1 (SD = 11.4) for the CBT group ($p < 0.005$ for both groups). No significant difference in mean AEP scores was seen between groups at any of the 4-week-interval assessments (see Table 2). Remission from depression was associated with lower AEP scores compared to continued depression for both the sertraline (36.5, SD = 10.4 vs 47.6, SD = 10.4; $p = 0.002$) and CBT (37.9, SD = 10.1 vs 52.4, SD = 9.3; $p < 0.0001$) groups.

Discussion

The results of our study indicate that major depression will remit in more than 50% of patients with epilepsy within 4 months of initiating treatment with either CBT or sertraline. In the intent-to-treat analysis using the primary outcome of remission determined by the MINI, with missing outcomes imputed to have continued depression, 52.8% (95% CI = ± 12) treated with sertraline and 60.3% (95% CI = ± 11.6) treated with CBT achieved remission. Attaining this degree of response in the sertraline group did not appear to require high doses for most subjects, with 55% on a daily dose of 100mg or less at the end of the study. These remission rates are comparable to other published results, such as the overall 47% remission rate from 7 randomized trials of major depression with over 600 subjects treated with SSRIs.²⁹ Both treatments were superior to our historical placebo-control group from 2 prior trials of depression in diabetes.^{27,28} This observation supports the recommendation by our NINDS review group to avoid a placebo-control group based on ethical considerations. Survival analysis of time to remission found a difference of <3 days between CBT and sertraline, which provides clinicians with evidence to support options for designing a therapeutic strategy specific to a patient's preferences and clinical requirements. For example, persons who are sensitive to adverse effects of central nervous system medications may be better suited for CBT, or those with transportation or mental health insurance limitations may prefer sertraline.

The association of increased risk of seizures with SSRIs in persons with epilepsy has been controversial. The FDA product labeling for sertraline, which is similar for most SSRIs, states that due to the increased risk of seizures, sertraline "should be prescribed with caution in patients with a seizure disorder."¹⁵ Recent cohort studies¹⁴ and case reports³⁰ continue to emphasize the potential of SSRIs for lowering the seizure threshold. The design and results of our study support the conclusion that sertraline does not have an increased risk of GTC seizures compared to nonpharmacological interventions for depression in persons with

epilepsy. We observed a trend toward fewer seizures of all types for both treatment groups, as was reported in a prior small study.³¹ We also found that mean monthly rates of focal seizures with impaired awareness and GTC seizures decreased in subjects who achieved remission from depression compared to a small increase in those with continued depression for both treatment groups, but the decrease was only significant for GTC seizures in the whole study cohort.

Although earlier studies suggested that sertraline may be associated with clinically significant adverse effects¹⁶ and subsequent worsening of quality of life,^{6,19} we did not observe this outcome. We also found no increased suicidal risk with sertraline compared to CBT. Regression analysis demonstrated that persistence of depression was the only significant predictor of suicidality compared to seizure rates, treatment assignment, or initiation of a new antiseizure medication.

Limitations of the study include the lack of blinding of treatment assignment for subjects and investigators for practical reasons. Investigators were blinded to the results of outcome assessments, and most measures were obtained with standardized self-report instruments. Although we did not include a placebo control group at the request of the NINDS review section based on ethical considerations, a recent systematic review of 5 randomized control trials of CBT in depression and epilepsy found that only 10.2% of waitlist controls showed significant improvement,¹³ which was less than the 23% remission rate in the historical control group used in our power analysis. Although the AEP is a valid and reliable tool for medication side effects, we found that improved depression was associated with better AEP scores, potentially confounding the assessment of medication effects as previously reported.¹⁷ The baseline seizure rate was a retrospective estimate of seizure occurrences in the past 3 months, which may have been subject to recall bias. Although most patients used monthly seizure calendars prior to the study, the baseline estimate may be less accurate than the prospective calendars obtained during the study. Seizures can vary over time, which may limit generalization of our findings due to the study's relatively small sample size and duration. Also, the depression results may not be generalizable to all clinical settings because the study was performed in academic centers with experienced therapists providing CBT. However, CBT was performed in a standardized protocol that is widely available to therapists.²¹

In summary, the trial results support that more than one-half of patients with epilepsy and depression will experience remission of depression and improved quality of life following treatment with either sertraline or CBT. Sertraline was not associated with worsening of seizures or suicidality. Remission from depression was associated with a reduction in GTC seizures. These findings should support efforts by clinicians to effectively treat depression in persons who are also experiencing the complex medical and psychosocial effects of epilepsy.

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FIGURE 1:

Enrollment, randomization, and follow-up of study participants. BDI = Beck Depression Inventory; CBT = cognitive behavior therapy; CES-D = Centers for the Epidemiologic Studies Depression scale; M.I.N.I. = Mini International Neuropsychiatric Interview.

FIGURE 2:

Time in depression for sertraline and cognitive behavior therapy groups. There was no difference in remission time between groups (log-rank test, $p = 0.79$). BDI = Beck Depression Inventory.

FIGURE 3:

Quality of Life in Epilepsy Inventory-89 (QOLIE-89) mean total scores. There were no significant differences between groups at any assessment. All within-group comparisons between screen and subsequent weeks were significant at $p < 0.008$. CBT = cognitive behavior therapy.

TABLE 1.

Demographic and Clinical Characteristics of Participant Groups

Characteristic	Sertraline	Cognitive Behavior Therapy
Total population, n	72	68
Female sex, n (%)	36 (50%)	41 (60%)
Mean age, yr (SD)	40.1 (10.7)	39.1 (12.1)
Race, n (%)		
White	59	58
African American	10	8
Asian	2	1
Other	1	1
Ethnicity, n (%)		
Hispanic	1	4
Non-Hispanic	71	64
Years of education (SD)	14.3 (3.0)	14.1 (2.4)
No prior treatment for depression, n (%)	64 (88.9%)	63 (92.6%)
Epilepsy classification, n (%)		
Focal	42 (58%)	36 (53%)
Generalized	7 (10%)	16 (23%)
Not definite	23 (32%)	16 (24%)
Antiepileptic medications, n (%)		
Lamotrigine	33 (45.8%)	22 (32.4%)
Levetiracetam	31 (43.1%)	22 (32.4%)
Zonisamide	14 (19.4%)	17 (25.0%)
Carbamazepine	8 (11.1%)	13 (19.1%)
Valpoic acid	9 (12.5%)	11 (16.2%)
Topiramate	11 (15.3%)	11 (16.2%)
Phenytoin	9 (12.5%)	10 (14.7%)
Total antiseizure medications, n		
1	22	31
2	32	21
3	15	8
4	2	5
5		1

No significant differences between groups.

SD = standard deviation.

TABLE 2.

Depression, Adverse Effects Profile, Quality of Life, and Seizure Outcomes

	Baseline		Week 8		Week 16	
	CBT	Sertraline	CBT	Sertraline	CBT	Sertraline
Beck Depression Inventory II	26.9 (10.5), n = 68	24.2 (8.4), n = 72	15.9 (10.8), n = 49 ^a	13.4 (8.6), n = 55 ^a	12.8 (11.9), n = 58 ^a	12.3 (9.9), n = 59
CES-D	30.5 (10.6), n = 67	30.5 (11.0), n = 72	17.4 (11.7), n = 50 ^a	15.1 (10.8), n = 56 ^a	14.1 (12.1), n = 58 ^a	13.0 (11.0), n = 60 ^a
Adverse events profile	47.4 (7.9), n = 63	48.1 (8.1), n = 72	41.9 (10.6), n = 50 ^a	39.2 (9.9), n = 56 ^a	41.1 (11.4), n = 58 ^a	39.0 (11.4), n = 60 ^a
QOLIE-89	50.1 (13.6), n = 63	51.5 (14.9), n = 71	58.3 (17.0), n = 48 ^a	64.4 (16.0), n = 56 ^a	63.0 (18.4), n = 59 ^a	66.1 (17.7), n = 59 ^a
Focal impaired seizures/mo	7.1 (26.4), n = 38	2.3 (4.7), n = 45	3.1 (11.4), n = 33	0.5 (1.5), n = 42 ^b	3.8 (13.3), n = 32	0.8 (4.5), n = 41
Generalized tonic-clonic seizures/mo	0.3 (0.6), n = 55	0.3 (0.7), n = 57	0.1 (0.5), n = 40	0.0 (0.15), n = 46 ^a	0.1 (0.2), n = 48 ^b	0.1 (0.3), n = 48

For BDI, CES-D, and AEP, higher scores indicate more severe depression or side effects. For the QOLIE-89, higher scores indicate better quality of life.

All values are mean (standard deviation).

No significant differences were found between treatment groups for any interval outcome measure.

^a $p < 0.005$ and

^b $p < 0.05$ for within group difference compared with baseline score.

AEP = Adverse Events Profile; BDI = Beck Depression Inventory II; CBT = cognitive behavior therapy; CES-D = Centers for the Epidemiologic Studies Depression Scale; QOLIE-89 = Quality of Life in Epilepsy Inventory-89.

TABLE 3.

Means and Medians for Time to Remission of Depression

Treatment	Mean ^a		Median	
	Estimate, wk	Standard Error	Estimate, wk	Standard Error
Setraline	8.9	0.74	8.0	1.3
Cognitive behavior therapy	9.3	0.76	9.0	1.2
Overall	9.1	0.53	8.7	0.95

No significant between group differences.

^aEstimation is limited to the largest survival time if it is censored.

TABLE 4.

Adverse Events Reported by 5% of Subjects in Either Treatment Group

Adverse Event	Cognitive Behavior Therapy, n = 68	Sertraline, n = 72
Anxiety	0	4
Chest pain	4	2
Cold	6	4
Diarrhea	0	10
Dizziness	5	8
Dry mouth	1	4
Headache	14	22
Insomnia	7	16
Memory difficulty	4	3
Muscle strain/pain	7	9
Nausea	4	11
Rash	1	5
Sexual dysfunction	0	4
Shakiness	1	13
Tiredness	8	30
Unsteadiness	3	5
Worsening depression	5	6