Original Investigation

Multicenter Pilot Treatment Trial for Psychogenic Nonepileptic Seizures
A Randomized Clinical Trial

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IMPORTANCE There is a paucity of controlled treatment trials for the treatment of conversion disorder, seizures type, also known as psychogenic nonepileptic seizures (PNES). Psychogenic nonepileptic seizures, the most common conversion disorder, are as disabling as epilepsy and are not adequately addressed or treated by mental health clinicians.

OBJECTIVE To evaluate different PNES treatments compared with standard medical care (treatment as usual).

DESIGN, SETTING, AND PARTICIPANTS Pilot randomized clinical trial at 3 academic medical centers with mental health clinicians trained to administer psychotherapy or psychopharmacology to outpatients with PNES. Thirty-eight participants were randomized in a blocked schedule among 3 sites to 1 of 4 treatment arms and were followed up for 16 weeks between September 2008 and February 2012; 34 were included in the analysis.

INTERVENTIONS Medication (flexible-dose sertraline hydrochloride) only, cognitive behavioral therapy informed psychotherapy (CBT-ip) only, CBT-ip with medication (sertraline), or treatment as usual.

MAIN OUTCOMES AND MEASURES Seizure frequency was the primary outcome; psychosocial and functioning measures, including psychiatric symptoms, social interactions, quality of life, and global functioning, were secondary outcomes. Data were collected prospectively, weekly, and with baseline, week 2, midpoint (week 8), and exit (week 16) batteries. Within-group analyses for each arm were performed on primary (seizure frequency) and secondary outcomes from treatment-blinded raters using an intention-to-treat analysis.

RESULTS The psychotherapy (CBT-ip) arm showed a 51.4% seizure reduction ($P = .01$) and significant improvement from baseline in secondary measures including depression, anxiety, quality of life, and global functioning ($P < .001$). The combined arm (CBT-ip with sertraline) showed 59.3% seizure reduction ($P = .008$) and significant improvements in some secondary measures, including global functioning ($P = .007$). The sertraline-only arm did not show a reduction in seizures ($P = .08$). The treatment as usual group showed no significant seizure reduction or improvement in secondary outcome measures ($P = .19$).

CONCLUSIONS AND RELEVANCE This pilot randomized clinical trial for PNES revealed significant seizure reduction and improved comorbid symptoms and global functioning with CBT-ip for PNES without and with sertraline. There were no improvements in the sertraline-only or treatment-as-usual arms. This study supports the use of manualized psychotherapy for PNES and successful training of mental health clinicians in the treatment. Future studies could assess larger-scale intervention dissemination.

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Psychogenic nonepileptic seizures (PNES) are a somatoform conversion disorder manifesting as paroxysmal events not associated with electroencephalographic (EEG) epileptiform correlates, and they have psychological underpinnings.[1] They are not responsive to treatment with, and may be worsened by, antiepileptic drugs.[2,3] They occur worldwide, and in the United States up to 20% of civilians and up to 25% of veterans diagnosed as having epilepsy actually have PNES,[4] making PNES as common as multiple sclerosis and Parkinson disease[5] and as disabling as epilepsy.[6] The phenomenology and psychological underpinnings of PNES are well delineated, including an understanding of risk factors and prognostic features.[7] Much less is known, however, about effective treatments for PNES, resulting in many patients returning to neurology offices and emergency departments because of recurrent seizures. Surveys administered to American Epilepsy Society members and UK clinicians described standard medical care (treatment as usual [TAU]) for PNES as a neurologist sharing the diagnosis with the patient and family, if present, while continuing to follow up with the patient, tapering the antiepileptic drug in lone PNES, and the majority not initiating psychotropic treatment but making a referral to a psychiatrist or psychologist.[8,9] Many times after diagnosis, patients with PNES do not pursue mental health care follow-up or they receive only supportive psychotherapy, which is not effective for PNES[10] or for depression.[11,12]

Prior pilot treatment trials revealed that sertraline hydrochloride or cognitive behavioral therapy (CBT) may be effective in reducing PNES. Patients receiving sertraline reported a 45% reduction in PNES, compared with an 8% increase in PNES in the placebo group.[13] An open-label psychotherapy study for PNES[10] used an epilepsy therapy workbook[14] modified to target dysfunctional cognitions and behaviors in patients with PNES.[15] Eleven of 17 individual therapy intervention completers (65%) reported no seizures by the end of the 12-week trial. The 12-session, therapist-guided seizure treatment workbook focused on gaining control of seizures and included training in healthy communication, understanding medications, conducting functional behavioral analysis, and examining internal and external triggers. In addition to seizure reduction, mean scores on scales measuring depression, anxiety, somatic symptoms, quality of life (QOL), and psychosocial functioning showed improvement from baseline to the final session, suggesting that the intervention also improved psychiatric symptoms, QOL, and functioning.

Despite PNES (formerly referred to as *pseudoseizures* or *hysteroepilepsy*) being recognized for centuries,[16] a fully powered phase 3 intervention randomized clinical trial (RCT) has not yet been conducted. Although the National Institutes of Health Epilepsy Benchmarks identified developing evidence-based treatment for PNES as a priority,[17] no standards for a generalizable, effective, widespread treatment for PNES are available. Thus, we have conducted a pilot RCT designed to evaluate various treatments for PNES. The secondary aims of the study included evaluating the impact of treatment on psychiatric symptoms, QOL, coping, and general and relational functioning and assessing the ability to disseminate the treatment to other sites.

Methods

The study was approved by the organizing site, Rhode Island Hospital, and by the Stanford University and University of Cincinnati institutional review boards. All enrollees provided written informed consent.

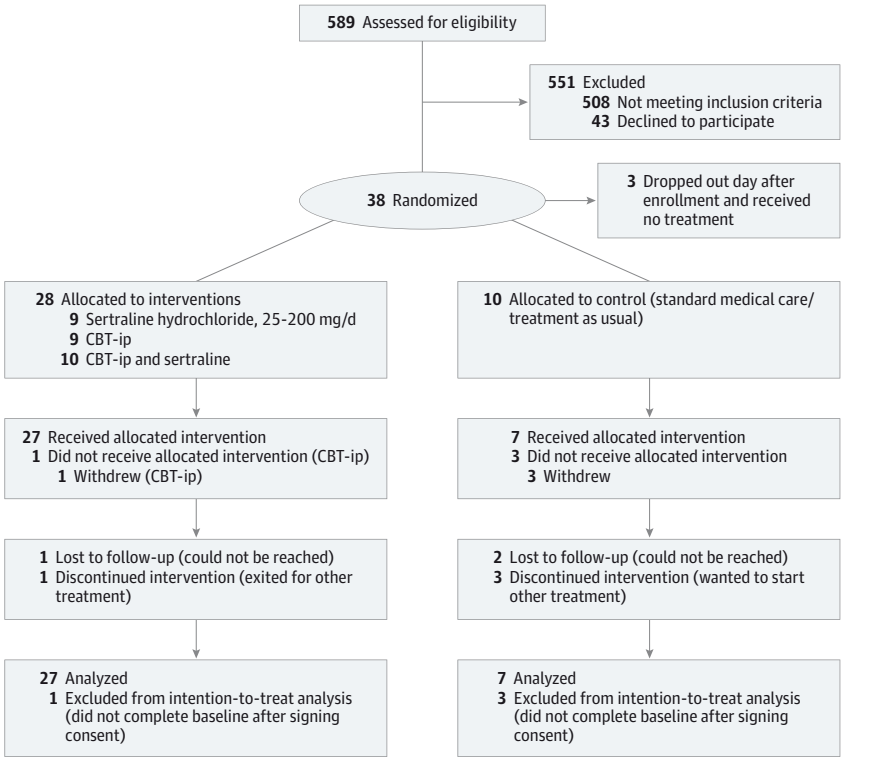
Participants aged 18 to 65 years with a video EEG-confirmed diagnosis of lone PNES and at least 1 event in the month prior were recruited between September 2008 and February 2012 (**Figure 1**). Criteria for the diagnosis of events consisted of stereotypic motor manifestations with or without change in level of consciousness.[18] Exclusion criteria included the following: concurrent mixed epilepsy and PNES or equivocal video EEG findings in discerning between epileptic seizures and PNES; use of monoamine oxidase inhibitor or pimozide within 30 days prior to study entry; current use of sumatriptan succinate or other serotonin 1 receptor agonist; allergy or sensitivity to sertraline; current enrollment in CBT for PNES; current or past-year self-mutilation; frank psychosis; current suicidality with intent to harm self; serious illness; active substance or alcohol use or dependence that could interfere with participation; pending litigation; and current application for long-term disability.

Study Design

Participants were randomized 1:1:1:1 into 1 of 4 treatment arms using a computer-generated blocked randomization. Enrollment was at Rhode Island Hospital initially (n = 28) and continued in 2010 when 2 other sites were added (Stanford University, n = 7; University of Cincinnati, n = 3), as designed in the dissemination infrastructure grant. Patients were randomized to psychotherapy for seizures (CBT informed psychotherapy [CBT-ip]; n = 9), flexible-dose sertraline (n = 9), combined CBT-ip and sertraline (n = 10), or TAU (n = 10). Sertraline was chosen because of its limited drug-drug interactions with antiepileptic drugs and because of its US Food and Drug Administration indications for the many diagnostic comorbidities occurring with PNES (eg, depression, anxiety, posttraumatic stress disorder).

A complete history and medical, psychiatric, and neurological examinations were obtained before or at enrollment. Clinician-rated assessments and self-report questionnaires measuring psychiatric symptoms, social interactions, QOL, and global functioning were given at baseline, treatment initiation (week 2), midpoint (week 8), and exit (week 16). As is the case in all seizure trials and because seizures are the source of disability, seizure frequency was selected as the primary outcome.[19] Seizure frequency was assessed daily using weekly seizure calendars, with family assisting participants in logging seizure frequency, triggers, and medical care utilization. Sertraline hydrochloride was started on day 14 and titrated up to 200 mg or as tolerated. The psychotherapy was administered in 12 weekly, 1-hour, individual sessions by 1 trained therapist per site starting on day 14 using the modified workbook from the previous open-label study.[10] Uniformity of treatment between sites was assured with pretreatment training; all therapists underwent one-on-one training with the prin-

Figure 1. CONSORT Flow Diagram of the Multisite Pilot Randomized Clinical Trial for Psychogenic Nonepileptic Seizures, Comparing Sertraline and/or Cognitive Behavioral Therapy Informed Psychotherapy (CBT-ip) With Treatment as Usual



cipal investigator (W.C.L.) on the CBT-ip intervention and treated 2 patients with PNES prior to the trial, with all sessions filmed for weekly feedback provided by the principal investigator. Participants in the TAU arm followed up with their treating neurologist and were seen biweekly for assessments, in the same manner as those in the other treatment arms. Throughout the study, therapy sessions from all sites were reviewed for treatment fidelity. Treatment providers demonstrated adherence and competence using a modified Cognitive Therapy Scale[20] and a Psychotherapy Rating Scale[21] used in the prior trial[10] before delivering treatment and during treatment across sites. Video EEG diagnosis between the 3 sites was independently validated, with excellent interrater reliability ($\kappa = 1.00$). Participants also provided comments and feedback in exit interviews, which were assessed using qualitative methods.

Self-report assessments included the Beck Depression Inventory-II, Beck Anxiety Inventory, Barratt Impulsiveness Scale, Davidson Trauma Scale, Dissociative Experiences Scale, Side Effects Profile, Symptom Checklist 90, Quality of Life in Epilepsy Inventory 31, QOL Burden to Family Scale, Expectations Scale, and Ways of Coping Questionnaire. Clinician-rated assessments included the Global Assessment of Functioning, Hamilton Depression Rating Scale, Oxford Handicap Scale, Clinical Global Impressions-Improvement, Clinical Global Impressions-Severity, and Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool (a quality-of-relationships measure). Treatment-blinded trained raters assessed clinician-scored outcomes after reliability was established. Interrater reliability was established by having raters score a sample of the same patients and having the results reviewed. Given the nature of interventions delivery, clinicians in the study were not blinded to the intervention.

Statistical Analysis

Generalized linear mixed models for negative binomial and Poisson data were used to model seizure counts and emergency department visits, respectively, as a function of treatment condition and time (PROC GLIMMIX; SAS version 9.3 statistical software; SAS Institute, Inc). Classic sandwich estimation was used to adjust for any model misspecification. This analysis technique was chosen because of its versatility in modeling individual trajectories of count data over time.

Linear trends were used to test significance of trajectories on secondary measures across the 4 ordinal assessment periods using PROC GLIMMIX. The linear trends across these ordinal assessments were compared between groups using orthogonal linear contrasts. For clinical relevance, difference means, 95% confidence intervals, and effect sizes are also presented.

Multiple comparisons were examined with orthogonal linear contrasts with α maintained at .05 using the Holm method. Because mixed modeling calculates individual trajectories for each participant and final seizure counts were unavailable for only 2 patients, this provided the intention-to-treat approach

Table 1. Patient Medical History Obtained by Interview and Record Review[a]

Characteristic	CBT-ip (n = 9)	CBT-ip With Sertraline (n = 9)	Sertraline (n = 9)	TAU (n = 7)
Sociodemographic, self-reported				
Age, mean (SD), y	37.9 (11.5)	39.1 (13.2)	39.7 (11.7)	41.6 (8.3)
Age at NES onset, mean (SD), y	33.6 (10.7)	36.7 (13.9)	33.2 (11.9)	39.1 (7.7)
Female, No. (%)	7 (77.8)	9 (100.0)	8 (88.9)	7 (100.0)
Education, mean (SD), y	15.4 (3.9)	15.7 (2.4)	13.0 (1.9)	16.0 (3.6)
Currently employed, No. (%)	2 (22.2)	6 (66.7)	2 (22.2)	2 (28.6)
Currently receiving disability, No. (%)	3 (33.3)	3 (33.3)	4 (44.4)	5 (71.4)
Currently married, No. (%)	4 (44.4)	6 (66.7)	4 (44.4)	2 (28.6)
Currently driving, No. (%)	3 (33.3)	0	3 (33.3)	3 (42.9)
Clinical diagnosis, made by neuropsychiatric examination and SCID, No. (%)[b]				
Mood disorders[c]	3 (33.3)	7 (77.8)	9 (100.0)	4 (57.1)
Anxiety disorders[d]	6 (85.7)	7 (87.5)	7 (100.0)	7 (100.0)
Somatoform disorders other than NES	1 (12.5)	3 (37.5)	2 (28.6)	3 (42.9)
Impulsivity, cluster B	1 (11.1)	1 (11.1)	3 (33.3)	2 (28.6)
Obsessive-compulsive personality disorder, cluster C	0	2 (22.2)	2 (22.2)	4 (57.1)
Clinical factors, from history at baseline				
History of trauma or abuse, No. (%)	7 (77.8)	6 (66.7)	7 (77.8)	6 (85.7)
Previous psychotherapy, No. (%)	6 (66.7)	6 (66.7)	5 (55.6)	3 (42.9)
Treated with psychotropic medications, past and current, No. (%)	8 (88.9)	8 (88.9)	9 (100.0)	5 (71.4)
Benzodiazepines, No. (%)	6 (66.7)	5 (55.6)	6 (66.7)	2 (28.6)
Antidepressants, No. (%)	4 (44.4)	7 (77.8)	6 (66.7)	5 (71.4)
Antipsychotics, No. (%)	2 (22.2)	1 (11.1)	0	2 (28.6)
On AEDs at baseline, No. (%)	5 (55.6)	5 (55.6)	7 (77.8)	3 (42.9)
Total lifetime AEDs, mean (SD), No.	2.67 (1.2)	4.00 (3.4)	3.11 (1.9)	4.00 (1.6)
Time from NES onset to NES diagnosis, y				
Mean (SD)	3.7 (4.6)	1.4 (1.3)	5.6 (5.6)	2.2 (3.4)
Median (range)	1.0 (0.0-10.6)	1.6 (0.0-3.7)	3.1 (0.2-14.4)	0.5 (0.1-9.5)
Time from NES diagnosis to NES treatment, y				
Mean (SD)	0.4 (0.7)	1.5 (2.6)	1.4 (2.2)	0.6 (1.2)
Median (range)	0.2 (0.0-2.1)	0.3 (0.0-7.0)	0.5 (0.1-6.9)	0.2 (0.04-3.4)
Abnormal neurological examination findings at enrollment, No. (%)	7 (87.5)	5 (55.6)	7 (87.5)	7 (100.0)
Abnormal brain MRI findings, past or at enrollment, No. (%)	3 (60.0)	4 (50.0)	4 (57.1)	3 (50.0)
30-min EEG tracing or video EEG findings, No. (%)				
Interictal epileptiform activity	0	0	1 (14.2)	0
Slowing, only EEG abnormality	0	2 (28.6)	1 (14.2)	0
Biological family history of seizures	2 (22.2)	3 (33.3)	2 (22.2)	3 (42.9)
History of head injury	3 (37.5)	5 (55.6)	6 (66.7)	7 (100.0)

Abbreviations: AEDs, antiepileptic drugs; CBT-ip, cognitive behavioral therapy informed psychotherapy; EEG, electroencephalography; MRI, magnetic resonance imaging; NES, nonepileptic seizures; SCID, Structured Clinical Interview for *DSM-IV* Disorders; TAU, treatment as usual.

[a] There were no significant differences between treatment groups in demographic and descriptive variables collected at enrollment.

[b] Not mutually exclusive.

[c] Seven patients have 2 different mood disorders.

[d] Four patients have 5 different anxiety disorders, 5 patients have 4 different anxiety disorders, 3 patients have 3 different anxiety disorders, 10 patients have 2 different anxiety disorders, and 6 patients have 1 anxiety disorder.

in the analyses. As a conservative effort, only 2-tailed tests and confidence intervals were calculated.

Results

A total of 81 patients met all inclusion and no exclusion criteria and were eligible from all 3 sites. Of the 81 eligible participants, 38 (46.9%) provided written informed consent for the study and 43 (53%) refused to participate (similar to rates of prior trials[10]). Three patients dropped out the day after signing consent, 31 completed all sessions and surveys, and 34 were included in the mixed modeling analysis to account for an intention-to-treat approach (Figure 1). The greatest reasons for screening failures included individuals not being eligible because of current comorbid epilepsy (n = 179 [35.2%]), lack of access (n = 111 [21.8%]), lack of seizure in the month prior to assessment (n = 29 [5.7%]), and not having a video EEG–confirmed diagnosis (n = 26 [5.1%]). Demographic characteristics, clinical factors, and clinical diagnoses are described in **Table 1**. There were no between-

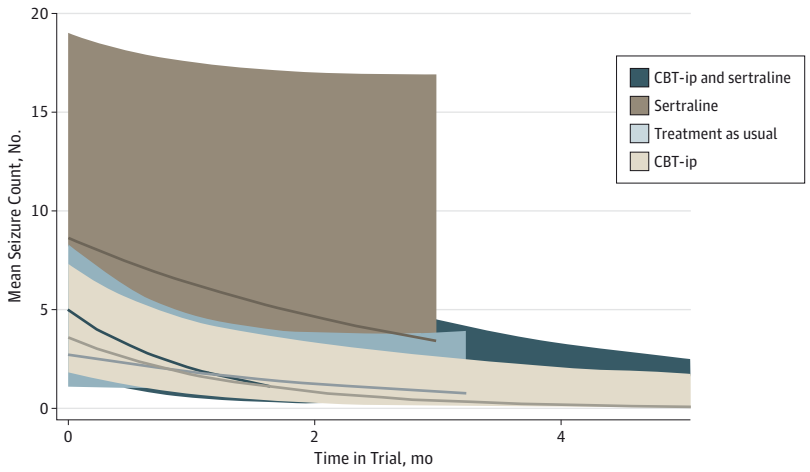
Table 2. Within-Treatment Condition Monthly Seizure Count Change

Treatment	Patients, No.	Slope (SE) [95% CI]	T_{438}	*P* Value	Posttreatment/Pretreatment Ratio of Seizures, Mean (SE) [95% CI]	Reduction, %
CBT-ip[a]	9	−0.72 (0.3) [−1.3 to −0.2]	−2.95	.01	0.49 (0.1) [0.28 to 0.84]	51.4
CBT-ip with sertraline[a]	9	−0.90 (0.3) [−1.6 to −0.2]	−2.69	.008	0.41 (0.1) [0.21 to 0.79]	59.3
Sertraline	9	−0.31 (0.2) [−0.6 to 0.03]	−1.78	.08	0.74 (0.1) [0.52 to 1.03]	26.5
Treatment as usual	7	−0.40 (0.3) [−1.0 to 0.2]	−1.32	.19	0.67 (0.2) [0.37 to 1.21]	33.8

Abbreviation: CBT-ip, cognitive behavioral therapy informed psychotherapy.

[a] Statistically significant differences.

Figure 2. Monthly Trajectory of Seizure Counts by Treatment Condition



Lines indicate functions of the mean weekly seizure count; shaded areas, variation corresponding to each line (treatment arm). Cognitive behavioral therapy informed psychotherapy (CBT-ip) with sertraline, *P* = .008; CBT-ip only, *P* = .01; sertraline only, *P* = .08; and treatment as usual, *P* = .19. Median time in the trial was 15 weeks, with a median range from 14 weeks in the sertraline group to 17 weeks in the group receiving CBT-ip only and the group receiving CBT-ip with sertraline.

treatment group significant differences in demographic variables at enrollment. Sample sizes did not allow for between-site analysis.

Primary Analysis of Treatment Effect on Seizure Frequency

Within-treatment condition analyses indicate significant reductions in the number of monthly seizures reported by patients in the CBT-ip condition and the CBT-ip with sertraline condition relative to prospective baseline. Specifically, patients in the CBT-ip condition reported 51.4% fewer total monthly seizures (*P* = .01) and patients in the CBT-ip with sertraline condition reported 59.3% fewer total monthly seizures (*P* = .008). Patients in the sertraline condition experienced 26.5% fewer total monthly seizures; however, this was not statistically significant (*P* = .08). Patients in the TAU condition did not experience a significant change in the total monthly number of seizures (*P* = .19). The pilot study was not powered to detect between-group differences and was designed for within-group analyses. A main effect was observed for time when modeling total seizures ($F_{1,30}$ = 17.44; *P* < .001). No interaction effect or between-treatment condition seizure trajectories were observed. These findings are summarized in **Table 2** and **Figure 2**.

The majority of patients in the 3 treatment conditions reported a 50% or greater reduction in the number of seizures from enrollment to exit (CBT-ip, 55.6%; CBT-ip with sertraline, 66.7%; sertraline, 55.6%). No change in seizures occurred in the CBT-ip (n = 1), CBT-ip with sertraline (n = 1), sertraline (n = 1), and TAU (n = 2) groups, and seizure increases were reported in the CBT-ip (n = 0), CBT-ip with sertraline (n = 1), sertraline (n = 4), and TAU (n = 2) groups. Several patients also reported seizure freedom (0 seizures) at the exit interview (CBT-ip, n = 3; CBT-ip with sertraline, n = 5; sertraline, n = 1; and TAU, n = 1 [excluding those with no seizures in the prospective baseline period]). When comparing patients who received CBT-ip with those who did not by combining conditions, the odds of achieving seizure freedom was 6.2 times greater for those receiving CBT-ip relative to those not receiving CBT-ip (*P* = .06).

Regarding patient expectations, a model examining seizure counts given treatment arm, time, and level of positive prognosis expectations (using a 1- to 5-point Likert scale at enrollment) did not yield a significant interaction effect. Thus, it does not appear that the level of self-predicted positive expectation influenced the effect of time and treatment arm for seizure count.

Treatment Effect on Secondary Outcomes

Secondary outcomes including depression, anxiety, somatic symptoms, QOL, impulsivity, and psychosocial functioning were examined within groups and between treatment conditions. Several between-group time-by-treatment interaction effects and main effects for time and condition were observed in secondary measures (eTable 1 in the Supplement). More importantly, results from multiple comparison tests indicate that when differences existed between treatment con-

Table 3. Between-Treatment Difference on Secondary Measures (Linear Trend)[a]

Treatment	Linear Trend Difference (SE) [95% CI]	T_{116}	*P* Value
Global Assessment of Functioning			
CBT-ip vs CBT-ip with sertraline	37.5 (20.9) [−18.5 to 93.6]	1.8	.37
CBT-ip vs sertraline	44.4 (25.0) [−22.7 to 111.5]	1.8	.37
CBT-ip vs treatment as usual[b]	66.8 (23.3) [4.3 to 129.3]	2.9	.03
CBT-ip with sertraline vs sertraline	6.9 (21.4) [−50.6 to 64.4]	0.3	.75
CBT-ip with sertraline vs treatment as usual	29.2 (19.4) [−22.8 to 81.3]	1.5	.40
Sertraline vs treatment as usual	28.1 (23.8) [−35.7 to 91.8]	1.2	.48
Oxford Handicap Scale			
CBT-ip vs CBT-ip with sertraline[b]	−4.2 (1.4) [−8.0 to −0.3]	−2.9	.02
CBT-ip vs sertraline[b]	−6.1 (1.9) [−11.3 to −0.9]	−3.1	.01
CBT-ip vs treatment as usual[b]	−6.3 (1.7) [−10.8 to −1.7]	−3.7	.002
CBT-ip with sertraline vs sertraline	−1.9 (2.0) [−7.2 to 3.4]	−1.0	.69
CBT-ip with sertraline vs treatment as usual	−2.1 (1.7) [−6.7 to 2.6]	−1.2	.69
Sertraline vs treatment as usual	−1.9 (2.2) [−7.7 to 4.0]	−0.9	.69
Clinical Global Impressions-Severity			
CBT-ip vs CBT-ip with sertraline	−2.5 (2.8) [−9.9 to 4.9]	−0.9	.69
CBT-ip vs sertraline	−5.8 (2.4) [−12.2 to 0.6]	−2.4	.09
CBT-ip vs treatment as usual[b]	−7.2 (2.2) [−13.1 to −1.2]	−3.3	.01
CBT-ip with sertraline vs sertraline	−3.3 (3.0) [−11.4 to 4.9]	−1.1	.69
CBT-ip with sertraline vs treatment as usual	−4.6 (2.9) [−12.4 to 3.1]	−1.6	.44
Sertraline vs treatment as usual	−3.1 (2.5) [−9.9 to 3.8]	−1.2	.69

Abbreviation: CBT-ip, cognitive behavioral therapy informed psychotherapy.

[a] Holm-Bonferroni method was used for tests of multiple comparisons.

[b] Statistically significant.

ditions, patients in the CBT-ip condition often improved more than those in the MED condition, the TAU condition, or both.

The study was not designed to randomize patients stratified on secondary measures at baseline. Nevertheless, treatment arms were found to be equivalent across secondary measures at baseline, with the exceptions of scores on anxiety, depression, and some somatic symptom scales, including the Beck Anxiety Inventory ($F_{3,24}$ = 3.43; P = .03), Beck Depression Inventory-II ($F_{3,30}$ = 4.38; P = .01), Hamilton Depression Rating Scale ($F_{3,24}$ = 3.25; P = .04), Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool ($F_{3,30}$ = 2.92; P = .05), and Side Effects Profile ($F_{3,30}$ = 4.38; P = .01). Multiple comparisons indicate that participants in the CBT-ip with sertraline group reported lower scores than those in the TAU group for the Beck Anxiety Inventory, Beck Depression Inventory-II, and Side Effects Profile; those in the CBT-ip with sertraline group also reported lower scores on the Beck Depression Inventory-II than those in the sertraline group. Multiple comparisons did not indicate differences between treatment arms for the Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool and Hamilton Depression Rating Scale. As a conservative effort, the potential moderating influence of these baseline differences on seizure count was therefore examined. However, no significant interactions were observed, indicating that the baseline differences on secondary measures did not have a moderating influence on seizure count (**Table 3**).

Linear trend estimates and standard errors on secondary outcomes were examined within each treatment condition relative to enrollment spanning 4 assessment periods (ie, baseline [enrollment], intervention initiation, midpoint, and final [exit]). Significant improvements were observed on most secondary outcomes for patients in the CBT-ip condition and several outcomes for patients in the CBT-ip with sertraline condition. No significant improvements were observed for patients in the sertraline condition. No measures improved in the patients in the TAU condition. As this is a pilot study, trends toward significance were also noted. Additionally, baseline and exit differential effect sizes were calculated for each condition. These results are summarized in eTable 2 in the Supplement, including categorical changes for the Ways of Coping Questionnaire. The eFigure in the Supplement includes mean plots of outcomes for secondary measures by treatment condition over the 4 assessment periods.

Qualitative reports from patient exit interviews revealed common themes found in the therapy groups, including appreciation for newly acquired coping skills (even if seizures did not abate completely), positive effects on relationships and activities, and medication adverse effects.

Lastly, generalized linear mixed models assuming a Poisson distribution comparing the number of emergency department visits prior to and during the trial (standardized by month) detected a significant time × treatment effect ($F_{3,60}$ = 4.81; P = .005). More importantly, Bonferroni multiple comparisons indicate that participants in the CBT-ip condition reported significantly fewer visits to the emergency department during the trial relative to baseline (estimated difference [SE], −1.3 [0.2]; t_{60} = 5.43; P < .001).

Discussion

In this pilot multisite RCT, a time-limited CBT-ip-based manualized intervention for PNES administered by trained clini-

cians resulted in significant reduction in PNES and improved comorbid psychiatric symptoms, QOL, and functioning. The psychotherapy arm showed significant improvements compared with TAU, which showed no improvements in primary or secondary outcomes. The secondary goal was to assess the feasibility of disseminating the treatment[10] to other locations and mental health clinicians.

Some studies of combined treatments for depression and anxiety showed greater benefit of combined psychotherapy and medication than either treatment alone.[22,23] The greater overall secondary outcome improvements in the CBT-ip–only arm, compared with the CBT-ip with sertraline arm, was unexpected. Given the trend in seizure reduction of 26.5% in the sertraline group (P = .08), we hypothesize that adding a selective serotonin reuptake inhibitor provides some reduction in seizures,[13] but medication adverse effects in this already somatically focused population may have mitigated its impact on the comorbidities. The selective serotonin reuptake inhibitor effects that may impact a fear-extinction domain[24] could have a differential effect on somatic symptoms. Qualitative review of patients on medication perspectives revealed statements such as, "My seizures are better, but I've had more upset stomach on the medication." The adverse effect–constitutional symptoms from the medication may have contributed to less reduction in the anxiety and depression scores than in the CBT-ip–only arm.

In addition to significant seizure reduction with the therapy, comorbid depression, anxiety, dissociation, and somatic symptoms also improved significantly. Given that comorbidities are the rule in the PNES population, the study was designed to take all comers; thus, we intentionally did not restrict inclusion based on common comorbidities (eg, posttraumatic stress disorder, anxiety, depression, Axis II traits and disorders, trauma history, family dysfunction) for external validity. The consistency of multiple comorbidities and stressors composes, in effect, the homogeneity of PNES. This intervention therefore treats patients with PNES, with all of their heterogeneities.[25]

Functioning, coping mechanisms, and QOL also improved. Patients in the CBT-ip (both alone and with sertraline) arms used unhealthy coping techniques at enrollment, and by exit they were using healthy techniques. The CBT informed therapy differs from supportive therapy, addresses traditional targets of CBT techniques (thoughts and schema), and incorporates interpersonal (targeting communication), mindfulness (targeting distress tolerance), and dynamic (targeting developmental) therapy methods that help develop healthy coping.[26] Drawing important techniques from other modalities accounts for its reach beyond solely treating seizures and differentiates this therapy from other treatments.[27] Although not powered to do so, the CBT-ip–only arm was significantly better than TAU for global functioning, Oxford Handicap Scale scores, and Clinical Global Impressions–Severity scores. Given improvements in the treatment groups contrasted against no improvements in the TAU group, the differences do not appear to be an effect of the natural course of the illness when patients had received other treatments.[28,29] That the effect was demonstrated with a small sample underscores the impact of the intervention.

Patients with seizures have travel limitations, and some patients receiving CBT-ip had to reschedule appointments because of transportation or weather. As was done in the pilot open-label trial,[10] Clinical Video Telehealth was used successfully again by the Rhode Island Hospital for 2 patients for sessions in this RCT when they had travel difficulties, and this did not affect participation or outcomes. The Veterans Affairs Medical Centers use Clinical Video Telehealth[30] for veterans with PNES. Tele–mental health care currently is not reimbursed by many insurance providers. Given the expense of this disorder in patients who receive inappropriate treatment,[31-34] Clinical Video Telehealth has the potential to improve access to care for civilians and should be assessed in a formal trial. Overcoming diagnosis and treatment obstacles (eg, transportation, providing treatment in remote areas), thereby addressing treatment gaps, could greatly reduce costs for the difficult-to-treat population. In this RCT, emergency department visits were significantly reduced in the CBT-ip arm, building on studies showing that identifying PNES decreases emergency department use.[35]

Our study gives the first level 1 data for PNES. Regarding level of evidence to inform evidence-based treatment[36] for PNES, while numerous open-label and uncontrolled trials are in the literature, to our knowledge the only 2 pilot RCTs for PNES include a traditional CBT approach (level 3 data)[37] or a pharmacologic approach (level 2 data).[13]

Limitations of the study were related to its sample size. This study was not an efficacy trial. Despite not being powered for differences between groups, however, the effect size demonstrated significant within-group reductions in seizures and differences between CBT-ip and TAU on secondary measures. While no demographic differences were present between groups, the CBT-ip with sertraline group and the TAU group showed baseline differences in anxiety, mood, and somatic symptom scale scores. Despite these differences, all groups were in the range of moderate to severe symptoms on scales at baseline. A larger sample size would likely diminish these differences with randomization. Furthermore, no baseline differences were observed for the primary outcome of seizure and most of the secondary variables, thus indicating that randomization occurred for these variables. Despite baseline differences in anxiety, depression, and somatic symptoms in 2 arms, these few differences did not moderate seizure count for the 4 arms. The trial was not double blind because it was not possible with some receiving CBT-ip, some receiving sertraline, some receiving CBT-ip with sertraline, and some receiving TAU. Blinding of the raters to treatment arm, however, provided blinded assessments. To reflect standard medical care in TAU, the study arms differed in that the TAU group received contact with mental health clinicians less frequently than the CBT-ip and CBT-ip with sertraline arms. Biweekly follow-up provided a modified exposure control (every 2 weeks in TAU vs weekly in therapy arms). Biweekly contact with the patients in the TAU condition was more frequent than the typical follow-up once every 1 to 3 months but was less frequent than in other arms. Contact was made, however, at the same frequency as the sertraline arm. Given the biweekly follow-up in both groups, with the sertraline arm showing some

improvements and the TAU arm showing no change or worsening, the differences are not attributable to less frequent contact in the TAU arm. The duration of follow-up for this study was linked to the treatment. We observed differences with CBT-ip; however, whether such responses are sustained over time (ie, whether freedom of PNES is maintained) is being assessed. The durability of the response will be assessed with 12-month follow-up examinations. Future trials could likewise assess outcomes of longer duration, eg, 6 or 12 months.

This study was a prelude to a trial planned to include a larger number of participants and outcome measures different from the traditional 50% responder rate (eg, seizure freedom). Choosing an appropriate outcome measure is germane to the overall success of such a study. While a 50% responder rate is the usual outcome measure in epilepsy regulatory trials, such an outcome measure may not be the most optimal one for PNES.[38] Thus, while providing important outcome data, this study also addressed several potential difficulties of conducting such trials in the PNES population, including participant recruitment and retention (good retention aided by contact with participants), choice of primary and secondary outcome measure(s), providing uniform treatments and intervention across centers, and training individuals on provision of interventions and collection of outcome data. While the study enrolled a relatively small number of participants, considering the financial limitations and the fact that significant resources were devoted to addressing the difficulties described, the study is significant not only for the outcomes but also because it trained and built a team of investigators across several institutions.

There are 3 stages to management of PNES: presentation of the diagnosis, gaining control of the seizures, and maintenance therapy.[27] Research reveals that most patients presented with the diagnosis of PNES do not have lasting improvement in their symptoms.[39] Maintenance therapies exist for other disorders and, although not yet studied, may be helpful for PNES. This study assessed the impact of treatments in the phase of gaining control and treatment. The durability of the treatment will be assessed in future studies. Patients who underwent this time-limited intervention noted that the treatment allowed them to gain control of their once seizure-dominated life and live a more normal life.

Conclusions

This pilot RCT for PNES demonstrates that this form of manualized psychotherapy for PNES reduced seizures and other somatic symptoms, improved psychiatric symptoms including depression and anxiety, and improved QOL, coping skills, and overall functioning. This study also demonstrates the feasibility of treatment dissemination to other sites.

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