Treating Patients with Psychogenic Nonepileptic Seizures

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Rhode Island Hospital
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American Epilepsy Society Annual Meeting
<table>
<thead>
<tr>
<th>Name of Commercial Interest</th>
<th>Type of Financial Relationship</th>
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</thead>
<tbody>
<tr>
<td>NINDS, AES, EF, Siravo Foundation</td>
<td>Grant support</td>
</tr>
<tr>
<td>Cambridge University Press</td>
<td>Editor’s royalties for Nonepileptic Seizures, 2010</td>
</tr>
</tbody>
</table>
Treatment for PNES

- PNES Treatments
  - NES Outcomes
  - NES Current Research
- PNES Future Directions
Terminology: Schematic representation of the nosological status of DCPNESD in relation with other mental disorders in DSM-IV.

(DCPNESD) Dissociation-Conversion Psychogenic Non-Epileptic Seizure Disorder

Post-traumatic stress disorder

Conversion disorder

Somatization and undifferentiated somatization disorder

Dissociative disorder NOS

(Marchetti et al. Seizure 2008;17;247-253.)
PNES and Gait Disorder
Mixed Epilepsy and PNES

(Papacostas. *EMG ClinNP* 2006;46:323)
Psychosocial factors in PNES

- Family
- Trauma/Abuse
- Cognitive/Somatic Distortions
- Mood, Anxiety, Impulsivity comorbidity
Family Functioning: FAD in patients

<table>
<thead>
<tr>
<th>Role</th>
<th>Epilepsy (n=108)</th>
<th>NES (n=99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affective Involvement*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affective Responsiveness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behavior Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Communication**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General functioning*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Problem Solving</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roles</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LaFrance 2010 (Krawetz, 2001)
## Abuse/Trauma in PNES

<table>
<thead>
<tr>
<th></th>
<th>All Subjects (N = 45)</th>
<th>Women (N = 35)</th>
<th>Men (N = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td><strong>%</strong></td>
<td><strong>N</strong></td>
<td><strong>%</strong></td>
</tr>
<tr>
<td>Sexual Abuse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>30  67</td>
<td>28  80</td>
<td>2  20</td>
</tr>
<tr>
<td>Pre-adult</td>
<td>26  58</td>
<td>24  69</td>
<td>2  20</td>
</tr>
<tr>
<td>Adult</td>
<td>16  36</td>
<td>16  46</td>
<td>0  0</td>
</tr>
<tr>
<td>Physical abuse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-adult</td>
<td>23  51</td>
<td>22  63</td>
<td>1  10</td>
</tr>
<tr>
<td>Spouse physical abuse</td>
<td>19  42</td>
<td>18  51</td>
<td>1  10</td>
</tr>
<tr>
<td>Any trauma</td>
<td>38  84</td>
<td>34  97</td>
<td>4  40*</td>
</tr>
</tbody>
</table>

(*P < 0.001)  
(Bowman, 1996)
Fear Sensitivity in PNES

(Hixson et al. E&B 2006;9:587-92)
## Association of Psychiatric Variables with PNES Outcome Class

<table>
<thead>
<tr>
<th>Psychiatric variable</th>
<th>Class I, n = 13</th>
<th>Class II, n = 12</th>
<th>Class III, n = 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent MDD</td>
<td>1 (8)</td>
<td>2 (17)</td>
<td>14 (70)</td>
</tr>
<tr>
<td>Personality disorder</td>
<td>1 (8)</td>
<td>3 (25)</td>
<td>16 (80)</td>
</tr>
<tr>
<td>Chronic abuse</td>
<td>3 (23)</td>
<td>1 (8)</td>
<td>16 (80)</td>
</tr>
<tr>
<td>Denial of psychosocial problems</td>
<td>0</td>
<td>8 (75)</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>
PNES and QoL

Fig. 1. (A) Mean scores and standard errors of a quality-of-life assessment survey (QOLIE-10). (B) Percentage of subjects noting improvements in QOLIE-10 subscales in the interval between diagnosis and follow-up interview.

(Quigg et al. Ep&Bhvr 2002)
Quality of Life and Epilepsy: AED Side Effects, Depression and Seizures

Quality of Life and PNES: Symptoms, Depression and Seizures

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“She is having another seizure, doctor.”
PNES: Treatment Outcome
Summary

- Complete **Resolution** of PNES
  19-83% (higher with early Dx/Tx)
- **Reduction** of PNES
  15-56%
- **No Change/Worsening** of PNES
  3-14%

- even with complete resolution
  1/3 to 3/4 remained **permanently disabled**

(Barry, 2001)
Outcomes in PNES from Reuber

- 71.2% continue to have PNES after a mean of 4 years from time of Diagnosis
- 56% were unemployed or tried to retire
- ~60% experienced PNES related injuries
- 51% initially had pseudo-status epilepticus
- 27.8% were admitted to ICUs
- 82% were readmitted to Neurology after Dx
- N=164, with mixed ES/PNES excluded

(Kanner, 2003)
PNES Treatments
Historically and Present

• Briquet, Charcot, Richer, Gowers: 19th - early 20th C
• Freud (Dream Analysis): early 20th C
• Hypnosis: early to late 20th C
• Psychotherapies: 20th C
• Medications: late 20th C

• Iatrogenic issues
Mean Dx Delay of PNES - 7 years
77% placed on AED prior to Dx
Drug toxicity found in 22%
55% of “pseudo-status” intubated
## Evidence Based Outcomes: Classifications

<table>
<thead>
<tr>
<th>Study Characteristic</th>
<th>Class of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
</tr>
<tr>
<td>Control Group</td>
<td>1</td>
</tr>
<tr>
<td>Representative Population</td>
<td>1</td>
</tr>
<tr>
<td>Assessment Independent of $R_x$</td>
<td>1</td>
</tr>
<tr>
<td>Blinded Outcome Assessment</td>
<td>1</td>
</tr>
<tr>
<td>Prospective Design</td>
<td>1</td>
</tr>
<tr>
<td>Randomized *</td>
<td>1</td>
</tr>
</tbody>
</table>

* Also meets standards of:
  - Primary outcomes defined;
  - Exclusion/inclusion criteria defined;
  - Dropout rate low and accounted for;
  - Baseline characteristics detailed and substantially equivalent.

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PNES Treatment Studies Review

24 publications in total

- 13 of which were case reports/case series
- 7 chart reviews or phone call follow-up
- 4 prospective, uncontrolled trials
  (all but 2 were class IV reports)

- No double blind, prospective, randomized controlled trials

(LaFrance & Devinsky. Epilepsia. 2004;45(sup2):15-21)
PNES Treatment Studies Review

- **Aboukasm** (1998) 61 patients in 4 groups, phone follow up Comprehensive Epilepsy Center Psychiatrist, Neurologist, NonCEP therapy, no feedback
- **Aldenkamp** (1989) 3 groups of 15, prospective, non-equivalent groups, inpatient behavioral, inpatient “watch and see”, and outpatient neurologist follow up
- **Ataoglu** (1998) 2 groups of 15, prospective, randomized trial of paradoxical intention therapy vs. diazepam
- **Goldstein** (2004, 2010) 20 and 66 patients, 12 sessions of cognitive behavioral therapy
- **Prigatano** (2002) 2 groups of 7/8 patients, 6 month group therapy
- **Rusch** (2001) retrospective review of 26 patients, found 6 symptom groupings and matched treatments.
PNES Treatment: Presentation of the Diagnosis

- 22 patients with PNES
- 10 patients with ES
- Retrospective, cohort study on Shen protocol
- Outcome: Number of events occurring within the 24-hour period after presentation of Dx
- Results: 18 of 22 PNES patients had no further events during acute follow-up period

(Farias, E&B, 2003)
NES Treatment:
Presentation of the Diagnosis
(the rest of the story…)

• 53 eligible PNES patients
• 23 of 52 completed a telephone survey
• mean post-Dx: 17 months (range 2-60 mos)
• 3 patients were seizure free.
• 15 had 50% reduction
• 20 of 23 (87%) still having PNES
• Responders – more likely to believe PNES dx and less likely to be on disability

What about AEDs in PNES?


- A number of articles show that AEDs are prescribed to patients with PNES inappropriately, with toxicity in 22% of patients (Krumholz, 1983).

- Oto et al (2005) showed that AEDs could safely be withdrawn in 64 outpatients with lone PNES. No SAEs.

- Duncan (2006) reviewed the literature and recommended that patients with lone PNES should be withdrawn from AEDs in an epilepsy center.
PNES Protocol: “Reframing the Diagnosis” and the role of Nursing

<table>
<thead>
<tr>
<th>PNES Outcomes: (seizure frequency at 2 yrs post Dx) (n=50)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No Seizures</td>
<td>24</td>
</tr>
<tr>
<td>Improved</td>
<td>19</td>
</tr>
<tr>
<td>No change</td>
<td>5</td>
</tr>
<tr>
<td>Not available for f/u</td>
<td>2</td>
</tr>
</tbody>
</table>

(Thompson, *Persp in Psy Care*. 2005;41:71-8)
What causes functional weakness?

Predisposing
- Biological: Genetic
- Psychological: Childhood adversity
- Social: Modelling

Precipitating
- Biological: Injury Disease
- Psychological: Emotional disorder
- Social: Life events (Home / Work)

Functional Weakness (or PNES)

Perpetuating
- Biological: Deconditioning CNS Plasticity?
- Psychological: Emotional disorder, Illness beliefs
- Social: Reinforcement of illness (family, money, doctors)

(Jon Stone, 2003, PMD Conference)
Modified Cognitive-behavioral model of pain-related fear (according to Vlayen & Linton (2000)).

(LaFrance & Bjørnæs, Nonepileptic Seizures, 3rd Ed. 2010)
Treatment of PNES Trials at RIH

- **8 week, open label pharmacologic trial**
- **16 week, double blind, randomized placebo-controlled trial** for treatment of PNES comorbid diagnoses
  - Captured PNES by vEEG
  - at least 1 NES per month
  - comorbid Depression, Anxiety, or Impulsivity disorder by SCID
  - Not on antidepressant at optimized dose for past month

- **Psychotherapy trial** for PNES - 4 month, randomized clinical trial of Cognitive Behavioral Therapy or Family Therapy for PNES

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(NINDS 5K23-NS PI: LaFrance)
Psychogenic Nonepileptic Seizures
Pilot Pharmacologic RCT
(n = 38) all enrollees, baseline evaluation

- **Demographics:**
  75% female, mean 36 years old, 47% married

- **Social:**
  High school education; 66% unemployed; 32% driving

- **Co-morbidities:**
  60% Mood disorders; 86% Anxiety disorders; 82% Abuse

- **Neurologic:**
  42% Abnormal Brain MRI; 29% Abnormal EEG; 43% Family History of seizures

(NINDS 5-K23-NS) (LaFrance et al. *Neurology*, 2010)
Pilot Pharm RCT for NES

Pilot pharmacologic randomized controlled trial for psychogenic nonepileptic seizures

ABSTRACT

Objective: There have been few treatment trials for psychogenic nonepileptic seizures (PNES). Some psychotherapies have been shown to improve PNES and comorbid symptom outcomes. We evaluated a pharmacologic intervention to test the hypothesis that sertraline would reduce PNES.

Methods: We conducted a pilot, double-blind, randomized, placebo-controlled trial in an academic medical hospital with epilepsy center outpatients. Subjects aged 18 to 65 years diagnosed with video-EEG-confirmed PNES were treated with flexible-dose sertraline or placebo over 12 weeks. Seizure calendars and symptom scales were charted prospectively. Secondary outcome measures included psychiatric symptom scales and psychosocial variables.

Results: Thirty-eight subjects enrolled, and 26 (68%) completed the trial. Thirty-three subjects with nonzero nonepileptic seizure rates at baseline were included in intent-to-treat analysis of the primary outcome. Subjects assigned to the sertraline arm experienced a 45% reduction in seizure rates from baseline to final visit ($p = 0.03$) vs an 8% increase in placebo ($p = 0.78$). Secondary outcome scales revealed no significant between-group differences in change scores from baseline to final visit, after adjustment for differences at baseline.

Conclusions: PNES were reduced in patients treated with a serotonin selective reuptake inhibitor, whereas those treated with placebo slightly increased. This study provides feasibility data for a larger-scale study.

Level of evidence: This study provides Class II evidence that flexible-dose sertraline up to a maximum dose of 200 mg is associated with a nonsignificant reduction in PNES rate compared with a placebo control arm (risk ratio 0.51, 95% confidence interval 0.25–1.05, $p = 0.29$), adjusting for differences at baseline. Neurology $2010;75:1166-1173$
Pilot Pharm RCT for PNES: Seizure frequency

Table 4: Mean and median psychogenic nonepileptic seizure frequency as a function of visit

<table>
<thead>
<tr>
<th>2-wk count at:</th>
<th>Placebo (n = 19)</th>
<th>Sertraline (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Median</td>
</tr>
<tr>
<td>Baseline (retrospective 2 wk prior)</td>
<td>11.3 (12.1)</td>
<td>6.0</td>
</tr>
<tr>
<td>Week 2 (prospectively collected from days 1-14)</td>
<td>8.9 (8.5)</td>
<td>6.0</td>
</tr>
<tr>
<td>Week 4</td>
<td>10.3 (10.6)</td>
<td>5.0</td>
</tr>
<tr>
<td>Week 6</td>
<td>10.9 (16.4)</td>
<td>3.0</td>
</tr>
<tr>
<td>Week 8</td>
<td>12.1 (17.4)</td>
<td>3.0</td>
</tr>
<tr>
<td>Week 10</td>
<td>11.7 (12.4)</td>
<td>7.0</td>
</tr>
<tr>
<td>Week 12</td>
<td>11.6 (14.0)</td>
<td>6.0</td>
</tr>
</tbody>
</table>

* Raw means and medians provided with standard deviation of biweekly seizure count. Overdispersed Poisson regression with return to baseline imputed for missing values at follow-up visit; no between-condition p values were significant at α = 0.05.
Cognitive behavioral therapy for psychogenic nonepileptic seizures

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Clinical trial

ABSTRACT

Treatment trials for psychogenic nonepileptic seizures (PNES) are few, despite the high prevalence and disabling nature of the disorder. We evaluated the effect of cognitive behavioral therapy (CBT) on reduction of PNES. Secondary measures included psychiatric symptom scales and psychosocial variables. We conducted a prospective clinical trial assessing the frequency of PNES in outpatients treated using a CBT for PNES manual. Subjects diagnosed with video/EEG-confirmed PNES were treated with CBT for PNES conducted in 12 weekly sessions. Seizure calendars were charted prospectively. Twenty-one subjects enrolled, and 17 (81%) completed the CBT intervention. Eleven of the 17 completers reported no seizures by their final CBT session. Mean scores on scales of depression, anxiety, somatic symptoms, quality of life, and psychosocial functioning showed improvement from baseline to final session. CBT for PNES reduced the number of PNES and improved psychiatric symptoms, psychosocial functioning, and quality of life.
### PNES Psychotherapy trial

#### Assessment Ratings at Baseline and Completion (N = 21; *Locf)  mean (sd)

<table>
<thead>
<tr>
<th>Scale</th>
<th>Cutoffs</th>
<th>Baseline</th>
<th>Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified Hamilton Depression Scale</td>
<td>[&lt;7]</td>
<td>14 (7)</td>
<td>11 (7)</td>
</tr>
<tr>
<td>Beck Depression Inventory-II</td>
<td>[&lt;14]</td>
<td>19 (15)</td>
<td>10 (7)*</td>
</tr>
<tr>
<td>Davidson Trauma Scale</td>
<td>[&lt;17]</td>
<td>58 (38)</td>
<td>36 (27)*</td>
</tr>
<tr>
<td>Barrett Impulsivity Scale</td>
<td>[&lt;70]</td>
<td>63 (14)</td>
<td>60 (9)*</td>
</tr>
<tr>
<td>Dissociative Experiences Scale</td>
<td>[&lt;5]</td>
<td>13 (12)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Symptom Checklist 90</td>
<td>[&lt;85]</td>
<td>94 (77)</td>
<td>62 (52)*</td>
</tr>
<tr>
<td>Global Assessment of Functioning*</td>
<td>[&gt;80]</td>
<td>50 (7)</td>
<td>59 (12)*</td>
</tr>
<tr>
<td>Oxford Handicap Scale</td>
<td>[&lt;2]</td>
<td>3.3 (1)</td>
<td>3.5 (1.2)*</td>
</tr>
<tr>
<td>QOLIE-31*</td>
<td>[&gt;63]</td>
<td>46 (24)</td>
<td>62 (19)*</td>
</tr>
<tr>
<td>Fam Assess Device: Gen Fxn Scr</td>
<td>[&lt;2.00]</td>
<td>2.03 (.57)</td>
<td>1.66 (.4)*</td>
</tr>
<tr>
<td>LIFE-RIFT (QoL measure)</td>
<td>[&lt;9]</td>
<td>12.9 (4)</td>
<td>11 (3.7)*</td>
</tr>
<tr>
<td>NES frequency during trial (Biweekly sum)</td>
<td></td>
<td>17 (23)</td>
<td>7 (14)*</td>
</tr>
<tr>
<td>NES Frequency (median)</td>
<td></td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

*p<0.05

Figure 1. Seizure frequency per week at baseline, month 1, and final visit

Mean Seizure Frequency
Median Seizure Frequency

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PNES Pilot Treatment Trials

• **PNES patients are symptomatic on a number of fronts**
  Hamilton Depression Scale; Symptom Checklist; Dissociative Experiences Scale; Family Assessment Device

• **PNES randomized treatment trials are feasible**
  PNES Cognitive Behavioral Therapy; PNES Pharmacotherapy Trial

• **Neuropsychiatric patient clinical research requires solutions that are complex, global, and multi-disciplinary**
  Neuropsychiatrist, Epileptologist, Psychologist, Biostatistician

(LaFrance et al. AES Abstract *Epilepsia* 2008)
LaFrance 2010


Introduction:
Introduction for the Patient: Understanding Seizures

Week 1:
Making the Decision to Begin the Process of Taking Control

Week 2:
Getting Support

Week 3:
Deciding about your Medication Therapy

Week 4:
Learning to Observe your Triggers

Week 5:
Channeling Negative Emotions into Productive Outlets

Week 6:
Relaxation Training

Week 7:
Identifying your Pre-seizure Aura

Week 8:
Dealing with External Life Stresses

Week 9:
Dealing with Internal Issues and Conflicts

Week 10:
Enhancing Personal Wellness: Learning to Reduce Tensions

Week 11:
Other Seizure Symptoms

Week 12:
Taking Control: An Ongoing Process
Interdisciplinary PNES Research

Available online at www.sciencedirect.com

Epilepsy & Behavior

Review

Nonepileptic seizures treatment workshop summary

W. Curt LaFrance Jr. *, Kenneth Alper, Debra Babcock, John J. Barry, Selim Benbadis, Rochelle Caplan, John Gates, Margaret Jacobs, Andres Kanner, Roy Martin, Lynn Rundhaugen, Randy Stewart, Christina Vert, for the NES Treatment Workshop participants

Brown Medical School, Departments of Neurology and Psychiatry, Rhode Island Hospital, 593 Eddy Street, Providence, RI 02903, USA.

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PNES: *Primum no nocere*

“Hard-to-treat patients may engender feelings of powerlessness, frustration, and mistrust in their treaters, which, if unprocessed, may lead to a poor relationship and excessive use of medications, tests, and procedures.”

(Stonnington CM et al. *AJP*. 2006;163:1510)
Neuropsychiatric Treatment of Nonepileptic Seizures (PNES)

I. Proper diagnosis: History and inpatient video EEG

II. Presentation: of PNES to patient and family

III. Psychiatric Treatment:
   A. Problem List identifying:
      Predisposing factors
      Precipitants to seizures
      Perpetuating factors
   B. informs Prescription of:
      1. Psychotherapy(ies) and/or
      2. Pharmacotherapy
         i. Tapering of AEDs (in lone PNES)
         ii. Titration of psychotropics

(LaFrance & Devinsky. Epilepsy and Beh. 2002;3(5) S19-23)
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Patients and their families

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