



Closing the Major Gap in PNES Research

Finding a Home for a Borderland Disorder

Brien J. Smith, MD, FAAN

Co-Chair, Department of Clinical Neurosciences, Spectrum Health Medical Group;

Director, Division of Clinical Neurosciences, Professor, College of Human Medicine, Michigan State University, Grand Rapids, MI

Address correspondence to: Brien J. Smith, MD, FAAN, XXXXX, 25 Michigan Street NE, Suite 6100, Grand Rapids, MI 49503. E-mail: Brien.Smith@spectrumhealth.org

Psychogenic nonepileptic seizures (PNES) are events commonly encountered by primary care physicians, neurologists, pediatricians, and emergency medicine physicians in their practices, yet there continues to be significant variability in the way they are evaluated, diagnosed, and treated. Lack of understanding this condition and limited data on long-term outcome from current treatment paradigms have resulted in an environment with iatrogenic injury, morbidity, and significant costs to the patient and healthcare system. This article will review the current state of research addressing PNES treatment both in the adult and pediatric populations.

PNES are events that resemble epileptic seizures but without concurrent epileptiform activity and with psychological underpinnings (1). The prevalence of PNES in the United States has been estimated to be 2 to 33 per 100,000 people (2), with a mean incidence of 3 per 100,000 people per year in those over age 18 (3). They account for 20 to 50 percent of EMU discharge diagnoses.

PNES have a psychological origin and are categorized as a type of conversion disorder. A conversion disorder is characterized by neurologic symptoms that are inconsistent with a neurologic disease and are not feigned (4); it is often associated with distress, disability, and a poor prognosis (5). There has been much debate about the classification and terminology of this disorder because of lack of consensus and proposed changes for DSM-V (6, 7). Currently by DSM-V, PNES will be classified with the diagnosis of conversion disorder (functional neurological symptom disorder) with a specific symptom type of attacks or seizures, found under a new category called somatic symptom and related disorders. (<http://dsm.psychiatryonline.org>)

Diagnosis

Over the last 30 years, there has been significant progress in identifying patient and seizure characteristics that would declare the diagnosis of PNES. At times, diagnosis of PNES can be challenging, but prolonged video/EEG monitoring has become the gold standard, and only infrequently are there diagnostic questions remaining after this procedure is appropriately completed. In a recent publication, the International League

Against Epilepsy Nonepileptic Seizures Task Force provided a comprehensive report summarizing diagnostic approaches and levels of diagnostic certainty (possible, probable, clinically established, and documented) (8). Misclassification or misdiagnosis of PNES can occur when based on history alone or observation of a singular event. Other tests that may aid in the differentiation of epileptic seizures from PNES (prolactin levels and neuropsychological batteries) lack the specificity and sensitivity to replace video/EEG monitoring.

Treatment

From a practical perspective, questions being asked by neurologists and epileptologists after the diagnosis of PNES has been made and communicated include 1) what treatment options are available that are effective in the long term? and 2) who are the qualified caregivers who can provide that therapy? The ILAE Neuropsychobiology Commission asked a committee of experts to produce a detailed report on the treatment of PNES. This recent publication provided specific recommendations for the stages of management: making the diagnosis, presenting the diagnosis, gaining control of seizures, and management of seizures and life activities (9).

Regarding therapies that result in effective long-term outcomes, previous reports used seizure remission or significant seizure reduction as the primary measure for a successful outcome in the treatment of PNES. Several retrospective studies suggest that about one-third of patients will report that PNES have stopped without intervention when asked 3 to 6 months after diagnosis (9–13). The encouraging short-term outcomes are not matched by those seen over the longer term (9, 13–15). A study completed by Reuber et al. demonstrated that 71 percent of patients continued to have seizures just over 4 years from the time of diagnosis (14). Nearly half of the patients who became seizure free remained “unproductive”



(receiving health-related state benefits), remained disabled, and continued to have symptoms of psychiatric disorders, such as personality disorder, somatization, and dissociative tendencies. This study suggested seizure remission is not a comprehensive measure of good medical or psychosocial outcome in PNES and other measures—including those related to the specific condition, the particular patient group (children vs adult), psychosocial domains, or objective and subjective components—should be considered (16). Schmutz et al. suggested that PNES (dissociative seizures) must be recognized as a psychiatric symptom, representing only a sign of an underlying morbidity. In that light, the current paradigm wherein PNES is used as a primary diagnosis to establish predictiveness should be abandoned and replaced with research based on the underlying psychiatric disorders (17). If PNES represents a final symptomatic expression that can derive from diverse psychopathological mechanisms, understanding this diversity may help clinicians provide more tailored treatments based on the subgroup their patient's psychiatric comorbidity has been classified into.

LaFrance et al. (9) suggested a formal psychiatric assessment should be arranged and performed before initiating therapy. Ideally, this would be a mental health professional (i.e., neuropsychiatrist, psychiatrist, or psychologist) with previous experience in the field who is part of the team that has assessed and diagnosed the patient, and who is comfortable with that diagnosis and subsequent management of the condition and other somatoform disorders. Unfortunately, this arrangement is the exception more than the rule.

Research on Treatment of PNES

Despite recognition of PNES as a disorder described in the medical literature as early as the 1700s (formerly referred to as “hysterical seizure” or “pseudoseizure”) and despite major advances in diagnostic capabilities starting in the 1980s with the advent of video/EEG monitoring, PNES treatment has lagged significantly. This disorder is situated in the “borderlands,” between neurology and psychiatry. The lack of “ownership” of PNES by psychiatrists and other mental health professionals has been a major factor for the lack of therapeutic studies and advances (18). LaFrance and Devinsky (2004) suggested that future directions in PNES research include areas of diagnosis, prevention, and treatment. Hundreds of articles have been published that address ictal semiology, psychiatric comorbidities, neurological findings, psychological makeup, and neuropsychological testing. Most of these articles address characteristics that may aid in the diagnosis of PNES. Several publications include a description of clinical features that might be useful in differentiating PNES from epileptic seizures (19–22)—with the caveat that no one sign, symptom, or adjunctive test definitively differentiates PNES from epilepsy.

The need to develop effective treatments for patients with PNES has been widely recognized (23–26). In May 2005, an international group of researchers gathered for the NINDS/NIMH/AES-sponsored Nonepileptic Seizures Treatment Workshop to discuss development of treatments for patients with PNES (23). This workshop set the benchmarks for research in PNES and was key to addressing specific areas such as

pediatrics, presenting the diagnosis, classification, outcome measures, and design of treatment trials.

Psychotherapy

Psychotherapy is considered the recommended and best validated approach to treating PNES (27, 28). Unfortunately, many patients do not engage with a mental health provider and are not only lost to follow-up but also reinserted into the medical environment, where repeat testing, procedures, and therapies are often reinitiated. It is still unclear what type of psychotherapy is likely to achieve the best results. In addition to case reports of psychological interventions, a number of uncontrolled treatment studies have evaluated outcomes using broadly similar interventions, group therapy, or matched patients' symptomatology to the treatment received (23, 25, 29–32). Rational recommendations about treatment preferences are limited for lack of an evidence base from a fully powered randomized controlled trial (RCT) (9).

Cognitive behavioral therapy (CBT)-based approaches are the most commonly cited effective psychological treatment for PNES. Elements of CBT were included in a case series by Rusch et al. (33), but subsequent pilot RCTs completed by Goldstein (2010) and LaFrance (2013) have been described in more detail. In an initial open-label study, Goldstein et al. (2004) evaluated CBT based on a fear escape model, which focuses on cognitive, emotional, physiological, and behavioral aspects of PNES (34). A subsequent pilot RCT in which CBT was delivered over 12 sessions versus a group receiving psychiatric outpatient care, showed the CBT group to be approximately three times more likely to be seizure-free during the final 3 months of a 6-month follow-up period than was the treatment-as-usual group (outpatient psychiatric care) (35). LaFrance et al. (2009) reported the development of the CBT-informed model based on an approach designed initially to enhance self-control of *epileptic* seizures (36), with some modifications for PNES (37). After an initial open-label evaluation with 21 patients, a pilot multicenter RCT was completed, enrolling 35 patients randomized at three sites to one of four treatment arms: medication (sertraline) only, CBT only, CBT and medication combined, or standard medical care/treatment as usual (SMC) (38). The CBT-informed arm showed significant seizure reduction, improvement in functioning, and better scores on symptoms scales. Combined treatments showed improvements in seizure reduction and comorbidities, and medication alone improved depression. No improvements occurred in the SMC arm, underscoring that supportive therapy does not work for PNES (9, 38).

Psychodynamic therapy was described in some detail by Kalogjera-Sackellares (2004), in which trauma is considered a central feature in PNES (39). Cases treated with this model have no controlled data reported. Reuber and Howlett (2009) described psychodynamic interpersonal therapy (PIT) for PNES (40). Treatment in 50 patients showed reduction in seizure frequency and severity, decreased psychological distress, and improved quality of life. Although not tested in a RCT, data from patients undergoing PIT implied a long-term beneficial effect on seizures and was cost effective (41, 42).



Pharmacotherapy

Various pharmacologic treatments for PNES or comorbid conditions including anxiety, or psychiatric depressive disorders have been reported anecdotally in case reports, review articles, and book chapters. The National Institute of Neurological Disorders and Stroke (NINDS) funded a pilot randomized, controlled trial of a selective serotonin reuptake inhibitor versus placebo for patients with PNES. The primary hypothesis was to assess the magnitude of seizure frequency reduction by treatment with sertraline required to inform a power analysis for a full-scale RCT. Patients in the sertraline arm manifested a significant 45% decline in biweekly seizure rates versus the control subjects, who experienced an 8% increase. Given the small pilot nature of the trial, no definitive conclusion could be made regarding SSRI treatment in patients with PNES (43). Other open label trials have included diazepam, sertraline, and venlafaxine.

Other Interventions

In a pilot feasibility study which was not controlled, the delivery of a brief manualized psycho-educational intervention for PNES by health professionals with minimal training in psychological treatment was associated with higher rates of cessation of PNES when compared to previous studies describing the short-term outcome of the communication of the diagnosis alone (44). Hypnosis (45) and eye movement desensitization and reprocessing (EMDR) (46) have been studied in either single case studies or small group studies for PNES. Group therapy has shown some improvement in psychological well-being, while family therapy may be helpful when there is significant family dysfunction (9).

Pediatric PNES

Population-based data on the prevalence or incidence of PNES in the pediatric populations are lacking. Although the prevalence of PNES appears to be lower in children than in adults, it does increase with age through adolescence. A recent critical review and invited commentary was published on psychogenic nonepileptic seizures in children (47). Almost all published studies on PNES in pediatric populations have involved small samples, retrospective analysis of data, and a limited description of interventions. Reaching a correct diagnosis as early as possible and clear communication of the diagnosis to child *and family* may be essential components to achieve optimum outcomes (48). Many children may still need follow-up that provides a comprehensive, multidisciplinary approach that is individualized. A number of studies have reported on affected children's follow-ups, and these studies suggest that outcomes are more favorable than in adults.

Currently Funded Research

A search for currently funded research associated with PNES was undertaken through websites, including NIH RePorter (NIH/NIMH/NINDS, AHRQ, and CDC funded grants), the Department of Defense (DoD), PCORI, American Academy of Neurology (AAN), American Psychiatric Association (APA), or direct inquiry with the Epilepsy Foundation (EF) and the American Epilepsy Society (AES). The following funded grant(s) were identified:

NIH RePorter — Psychogenic nonepileptic seizures in U.S. veterans. Jan 2013–Dec 2016. The proposed research will provide detailed patterns of psychiatric illness associated with the development of PNES in U.S. veterans. It will also aid in the early recognition of PNES and the development of treatment strategies for PNES with the ultimate goal in reducing long-term disability. (PI: Martin Salinsky, VA MERIT grant)

Many clinicians associate PNES with patients (predominantly female) with a previous history of physical and sexual abuse. Recent work from the Veterans Affairs Medical Centers has changed this perspective when PNES was frequently encountered in their epilepsy monitoring units (EMUs), and an association with posttraumatic stress disorder (PTSD) was identified (49, 50).

No specific current funding for PNES was identified through research funding sources other than NIH RePorter. Prior studies have been conducted that were funded by NINDS, AES, and EF; however, they are not listed in this article.

Discussion

Two major issues surface regarding PNES research and clinical practice: The first is whether epileptologists can design and implement large, adequately powered, controlled, multicenter trials to provide definitive treatment for PNES without the direct engagement of psychiatrists and mental health professionals (17, 51–52). Many would argue no, that mental health providers are essential to collaborative care for patients with PNES. This deficit is underscored when there continues to be debate and disagreement on the basics such as consistent terminology, classification, billing and coding, and discussion on outcome measures and study design. Lack of overall interest in treating somatoform/conversion disorders and hesitancy of psychiatrists to be proactively engaged in the study design process, along with identifying and capturing major funding sources, have been major barriers (53). Focused efforts to improve training and education of functional neurological symptom disorders should help new generations of psychiatrists “embrace” the diagnosis, understand the reliability of video/EEG monitoring and become more involved in research and clinical practice.

The second issue relates to practice. What are some of the current practical clinical care model issues to be taken into consideration as we attempt to complete these important studies? Specifically, what has been done for early detection or prevention of PNES? We discuss the value of presenting the diagnosis, but what about the impact of subsequent transition of care from neurology to mental health providers? Does it actually limit the process when a consult liaison psychiatrist who completes the initial evaluation hands off to an outpatient partner, refers to an outside independent provider, or refers to community mental health provider (typically based on insurance and availability)? This process of “referring into limbo” is an even bigger concern when patients travel hours to an epilepsy center for monitoring, a PNES diagnosis is made, and they are told to follow up with a psychiatrist near their home. Limited communication among caregivers and the lack of personal connection perceived by the patient (transferring from one previously unknown caregiver to another) may cause the patient's confidence to spiral




downward about the therapeutic process. Often, a patient is sent to a healthcare worker they have never met, who may have very limited experience with conversion disorders, and who has no CBT expertise. These care pathway deficits clearly breach the concept of seamless, adequate care. Although, even under circumstances when patients are offered specialized, well coordinated care, patient engagement in treatment is often not optimal. Understanding the factors (patient versus provider related) that impact engagement and retention in treatment requires further investigation. Other concerns include whether the length of time to initiating therapy directed at PNES after diagnosis impacts outcome. Should we be engaging with centers for Medicare and Medicaid services (CMS)—similar to efforts in the field of dementia—to discuss program development to deliver healthcare that is person-centered, comprehensive, and interdisciplinary? Development of a national database could provide data leading to a significant reduction in healthcare costs and iatrogenic morbidity. Will a healthcare system support the development of comprehensive multidisciplinary care needed for this complex neuropsychiatric patient population? With the rapid changes in healthcare, budget belt-tightening in both academic and community environments, and administrators who continue to heavily weigh procedures and surgeries that provide positive return on investment, the availability of well-trained and experienced professionals to provide this service has been limited. Despite changes in favor of mental health parity, behavioral services continue to be placed low on the priority ladder in healthcare. In sum, there are numerous questions and challenges that need to be addressed proactively by members of neurology, mental health, and the research communities, and corporate healthcare for patients with PNES.

Conclusion

Psychogenic nonepileptic seizures, a common neuropsychiatric symptom, are frequently misdiagnosed, mistreated, and avoided by many healthcare providers. Guidelines on how to treat this complex patient population do not exist, owing to a lack of fully powered randomized, controlled trials evaluating the efficacy of different treatment modalities. Preliminary pilot studies suggest that CBT for PNES may improve outcomes, but funding for larger, fully powered, controlled trials has not occurred—in part because of the lack of priority given to PNES treatment development by those in the fields of psychiatry and neurology (51). Cooperation between neurologists and mental health professionals in multicenter frameworks is a requirement (17, 51–52) to provide an appropriate home for this “borderland” disorder.

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