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Review Article

Psychogenic Non-epileptic Seizures: An Updated Primer

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Background: *Psychogenic non-epileptic seizures are the most common paroxysmal event misdiagnosed as epilepsy. They significantly affect quality of life, functional status, and use of medical resources.* **Objective:** *The goal of this review is to provide guidance to psychiatrists and other mental health professionals in the understanding and practical management of this condition.* **Results:** *An abundance of new reports on the pathogenesis and effective treatments have become available over the last decade, yet specific barriers impede the fluid transition to treatment and remain an important challenge in the management of patients with psychogenic non-epileptic seizures. In the context of these difficulties, we initially present background information on psychogenic non-epileptic seizures covering their historic context, epidemiology, etiologic factors (including psychiatric, neuromedical, and neuropsychological factors), and current neurobiological models. Updated evidence-based treatments are discussed along with data on long-term outcomes. We also provide practical tools to help clinicians navigate differential diagnoses, establish their interdisciplinary roles, communicate the diagnosis, deliver treatment, and sort out commonly encountered challenges in the management of this condition.*

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INTRODUCTION

Psychogenic non-epileptic seizures (PNES) are sudden involuntary episodes of any combination of altered movement, sensation, or awareness that bear resemblance to epileptic seizures, but are not accompanied by epileptiform electrical discharges, and are presumed to be associated with a psychological origin. In the last decade, advances have been made in the neurobiological understanding and evidence-based treatments for this condition. Despite this progress, many barriers interfere with successful outcomes, as discussed in our "Challenges" section. The goal of this primer on PNES is to reach mental health professionals in charge of managing this condition, who are encouraged to assimilate the presented information in the context of the difficulties usually encountered in their practices. A broad range of topics related to PNES is covered in this review, including updated information and practical tools to help manage patients with PNES at their various stages of care. For more detailed background information on the topic, the reader should refer to the textbook *Gates and Rowan's Nonepileptic Seizures*,[1] currently in its third edition.

History and Nosology

PNES represent a neuropsychiatric condition that is at the intersection of neurology and psychiatry. Jean

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Martin Charcot, a French neurologist, characterized "hysteria" as a condition in which patients presented with similar impairments to those caused by identifiable brain lesions, but that were due to psychological trauma. Pierre Janet, Josef Breuer, and Sigmund Freud developed the concept of dissociation as a defense against psychological distress that is associated with memories of trauma, converted into somatic or cognitive symptoms and unconscious to the patient.[2]

Names previously given to this condition include hystero-epilepsy, pseudoseizures, and behavioral spells. These names have now been abandoned either because they are vague or pejorative. The accepted terms in the medical community are now "psychogenic non-epileptic seizures" (PNES) or "non-epileptic (or dissociative) attack disorder." The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) classifies PNES as a subtype of conversion disorder or functional neurological symptom disorder (FNSD).[3] Functional neurological symptoms are not voluntarily produced, but are rather presumed to be unconsciously elaborated. This differentiates FNSD from factitious disorder or malingering, which, by definition, requires the volitional elaboration of symptoms.[3]

Epidemiology

The incidence of PNES is estimated between 1.4 and 4.9 per 100,000 per year and the prevalence between 2 and 33 per 100,000.[4] Up to 30% of admissions to epilepsy monitoring units are diagnosed with PNES at discharge.[5]

The mean latency from initial manifestation to diagnosis is 5–7 years.[4] Episodes of recurrent, prolonged PNES (also called "non-epileptic psychogenic status" and defined as episodes lasting more than 30 min) occur in one-third of patients with PNES, with three-quarters of patients with PNES reporting at least one non-epileptic psychogenic status episode in their lifetime.[6]

The risk of misdiagnosis and iatrogenic complications from inappropriate treatment is substantial. PNES lead to a significant effect on quality of life, high rates of disability, excessive medical use, and unaddressed psychological problems.[6]

PNES can be seen across the age span, with onset occurring more commonly between the second and fourth decades of life.[7] They are more common in women at a ratio of 3:1 during their reproductive years.[8] PNES in the preadolescent and geriatric age groups are equally distributed between both sex groups.[8,9]

DIFFERENTIAL DIAGNOSIS

PNES is the most common condition mistaken as epilepsy. Epileptic seizures occur owing to abnormal excessive or synchronous neuronal activity in the brain. The clinical manifestations of epileptic seizures are diverse and anatomically related to the area of the brain affected by the seizure. Paroxysmal events that resemble epileptic seizures can have diverse etiologies. Table 1 summarizes the most common conditions to be considered when evaluating patients with paroxysmal episodes.

A structured interview acquiring a detailed semiologic description of the events strengthens the pretest probability of the diagnostic video electroencephalography (EEG) evaluation (the gold standard to establish the diagnosis). Noteworthy semiologic characteristics associated with PNES include preserved awareness during a bilateral motor event, eye fluttering, and responsiveness to bystander intervention during the event.[10] Other clinical signs of variable clinical significance include: prolonged (>2 min) motor events followed by complete recovery and a fluctuating course of motor phenomena. None of the clinical signs by themselves have a strong enough diagnostic value unless the psychiatric, neurological, and neurophysiologic backgrounds are taken into account.

As opposed to most epileptic seizures, EEGs acquired during PNES do not show electrographic changes supportive of epileptiform activity. Instead, the EEG during PNES reveals preserved background rhythms seen in normal EEGs and normal reactivity, often contaminated by the movement and muscle artifact during the event. There are epileptic seizures that show minimal or no changes in the EEG during the time of the spell; these seizures usually arise from areas of the brain (mesial or basal cortices of the brain) that are hard to sample with scalp EEG electrodes. Frontal lobe seizures may present a particular diagnostic challenge. Seizures arising from the dorsolateral aspect of the frontal lobe may have manifestations of activation of primary motor cortices such as forced eye version (contralateral activation of the frontal eye

TABLE 1. Differential Diagnosis of Paroxysmal Events

Condition/diagnosis	Clinical characteristics	Supportive tests
Epileptic seizures	Short duration (less than 2-5 min) Stereotypical (similar behavior and duration among events) Single or few event types in one single patient 70% respond to AEDs If the patient is unresponsive during the spell, he/she may be amnestic for part or the entire event May have warning symptoms or auras The patient may be confused after the event	EEG Video EEG monitoring
Syncope	Sudden loss of consciousness and postural tone Very short duration (seconds) Prodromal signs are frequent (lightheadedness, parlor, sweatiness, vision changes, muffled hearing) Cardiogenic syncope may be preceded by palpitations May be related to situations or positions (standing, rapid positional changes, urination, and having medical procedures) Rapid recovery on supine position Motor manifestations are frequent (myoclonus, version, and tonic postures), reported in 70–90% of studied syncopal events. These are more frequent if patient is kept on an upright position and are referred to as "convulsive syncope" Immediate recovery Post-event confusion is rare	ECG Holter ECG monitoring Tilt table test Autonomic testing
Parasomnias	Onset during sleep Dependent on the sleep stage, they tend to happen around the same portion of the night (REM behavior disorders or NREM parasomnias) Complex behaviors while asleep (eating, walking, engaging in activities, and acting out dreams) Behaviors are non-stereotypical activities Behaviors last minutes Patient has no or little recollection of the event NREM parasomnias typically start during childhood	PSG Video PSG with EEG
Narcolepsy with cataplexy	Excessive daytime sleepiness Cataplexy: Sudden transient episodes of loss of motor tone with preserved consciousness, usually in response to strong emotions Sleep-onset REM Sleep attacks during activities Hypnogogic hallucinations (vivid, bizarre or frightening dreams) Sleep paralysis	PSG MSLT
PNES	Multiple event types No or mild response to AEDs Longer duration than epileptic seizures (minutes to hours) Partial awareness or responsiveness during the event	Video EEG monitoring Neuropsychological evaluation
TIA	Episode of focal neurological dysfunction due to transient cerebral ischemia More likely in patients with vascular risk factors (age, elevated BP, diabetes, dyslipidemia) Usually negative symptoms (weakness, numbness, aphasia, etc.) Preserved consciousness Lasts minutes to hours Symptoms vary according to vascular territory compromised and the etiology of the TIA (low flow, embolic or small vessel occlusion) Recurrent TIA can be seen in situations of low flow Full stroke workup needed when TIA is suspected	Immediate CT head or Brain MRI and MRA Neurovascular ultrasound ECG Cardiac monitoring Echocardiogram Further studies according to the etiology of the TIA
Migraine with aura	Neurological symptoms may accompany migraine headaches Migraine auras are often progressive with subsequent complete recovery to baseline Aura lasts minutes to an hour Aura may precede the headache or follow it within 1 h	Diagnosis is clinical MRI may be indicated in presence of focal deficit on examination, initial

TABLE 1. Continued

Condition/diagnosis	Clinical characteristics	Supportive tests
	Migraine auras may have visual, sensory and more rarely motor or speech related manifestations Migraine headache is often: unilateral, moderate to severe, throbbing, worsens with exercise and may have associated nausea and or vomiting. Phonophobia or photophobia are common during attacks Special migraine subtypes include: Migraine with brainstem aura which can be associated with dysarthria, vertigo, tinnitus, diplopia, ataxia or decreased level of consciousness in addition to classic migraine auras Hemiplegic migraine has fully reversible motor weakness and fully reversible visual, sensory and or language symptoms	presentation, "worse headache" or no response to treatment

AEDs = antiepileptic drugs; BP = blood pressure; EEG = electroencephalogram; ECG = electrocardiogram; REM = rapid eye movement, NREM = non rapid eye movement; PSG = polysomnography; MSLT = multiple sleep latency test; CT = computed tomography; MRI = magnetic resonance imaging; MRA = magnetic resonance angiography; TIA = transient ischemic attack.

field), clonic or tonic movements, head version, or aphasia (when Broca's area is involved). Seizures arising from the prefrontal cortex have been described as "hypermotor seizures" and have variable clinical manifestations, including bizarre gestures, laughing, shouting, and alternating limb movements such as peddling and thrashing of the extremities.[11] Seizures originating from the cingulate gyrus can display complex stereotypic movements, such as kicking, grasping, or running, all with or without vocalizations. More complex behavior, such as aggression, delusions, and self-mutilation, are rare but have also been described. Seizures arising from the supplementary sensorimotor area in the mesial frontal region are characterized by sudden, brief, and asymmetric tonic posturing of one or more extremities with repetitive vocalizations; these seizures tend to occur in clusters.[12] These clinical manifestations may be reminiscent of PNES; however, even in the absence of clear EEG changes, epileptic seizures of frontal lobe origin tend to be brief, stereotypical, have a distinct onset and offset, often arise from sleep and have a brief postictal period.

PSYCHIATRIC ETIOLOGIC FACTORS

A multidimensional model emphasizes predisposing, precipitating, and perpetuating factors, in the development of PNES.[13,14] The Figure summarizes the interaction of these factors at different time points.

In DSM-5, the association of functional neurologic symptoms to a circumstantial trigger at the onset of the illness is no longer a requirement for the diagnosis, compared with the manual's previous edition. Circumstantial triggers are rather a specifier, which may be identified in some patients. The emphasis in DSM-5 is rather placed on the physiologic incompatibility between the presenting symptom and the examination or tests that prove this incongruency.[3]

Psychiatric Comorbidities

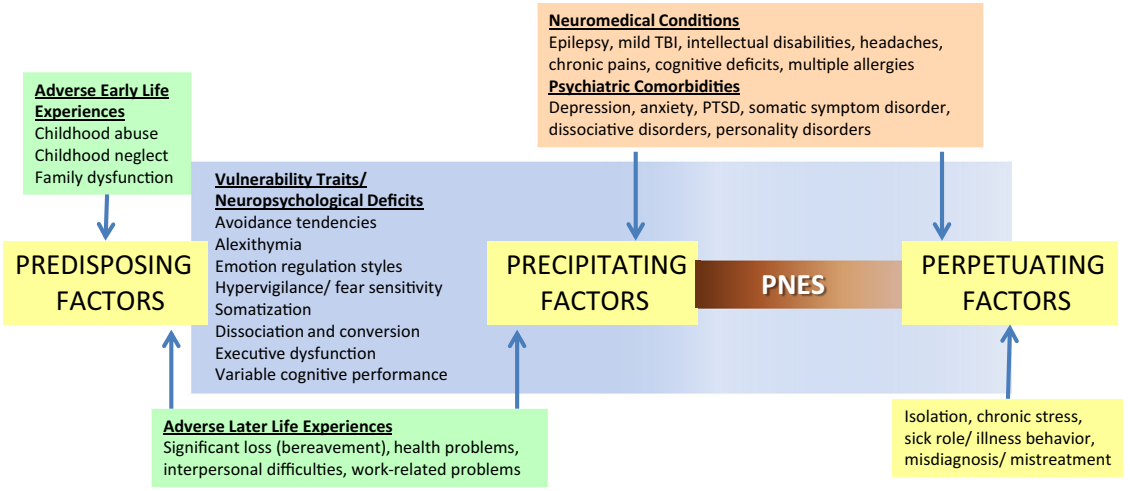
Patients with PNES suffer from a high rate of comorbid psychiatric conditions, particularly depressive disorders (57−85%), anxiety disorders including panic disorder (11–50%), posttraumatic stress disorder (PTSD) (35–49%), somatic symptom and related disorders including pain syndromes (22–84%), dissociative disorders (22–91%), and personality disorders (10–86%). They commonly suffer from other medically unexplained symptoms.[7]

The presence of psychiatric comorbidities has been correlated with more severe dysfunction and impaired quality of life in this population.[15] Lifetime rates of psychiatric disorders in epilepsy are lower than in PNES, although still higher than in the general population. This includes lifetime rates of depressive disorders of 10–50%, anxiety disorders including panic of 10–44%, and personality disorders of 15–40% in patients with epilepsy.[16,17]

Role of Trauma and PTSD

Traumatic lifetime experiences are commonly reported by adult patients with PNES. Childhood

FIGURE. Multiple Factors are Associated to PNES Including Vulnerability Traits/Neuropsychological Deficits, Adverse Life Experiences and Psychiatric Comorbidities and Neuromedical Conditions. These Factors Interact at Different Time Points as Predisposing, Precipitating, or Perpetuating. (Color version of figure is available online.)



physical abuse and sexual abuse are consistently the most frequently reported traumas, with rates ranging between 23% and 77%, followed by the loss of a significant other, psychological/emotional abuse and neglect, witnessing the abuse of others, and medical trauma.[18]

History of prior sexual abuse has been associated with early onset of symptoms, more severe events, and greater diagnostic delay. Sexual abuse, which is more common in women, may partially explain the gender distribution of the disorder.[18]

Childhood trauma is thought to play a less significant etiologic role in certain subgroups, such as pediatric populations (where exposure to other life adversities are more common), late adulthood onset individuals (where psychological trauma related to poor health has a more prevalent role), men (where work-related stressors have a more frequent etiologic influence), and patients with learning disability.[8,19,20]

Family Dysfunction

Families of patients with PNES have more frequent psychiatric disorders, epilepsy, health problems, higher tendency toward somatization, and higher criticism compared with families of patients with epileptic seizures.[7] The influence of family dynamics, although difficult to quantify, can become an important therapeutic target to minimize perpetuation of symptoms.

Emotion Processing

A number of deficits in emotion processing have been identified in PNES and they are presumed to be a major vulnerability trait that predisposes subjects to the development of conversion symptoms. A substantial number of PNES subjects score high on a self-report measure of alexithymia, a deficit in the recognition and verbalization of emotional states, with a tendency toward the physical expression of emotions.[21] PNES subjects also have difficulty in recognizing emotional factors as possible triggers for their episodes, further supporting a deficit in emotion recognition.

Fear sensitivity[22] and avoidance[23] have been identified in PNES. Both of these traits signal a potential psychopathological mechanism of increased autonomic reactivity coupled with a response style that limits acceptance and use of effective behavioral strategies in the face of emotional challenges.

Cluster analysis of emotion regulation profiles in PNES subjects has identified 2 major subpopulations. One subgroup is characterized by emotion "undermodulation" and presents with increased emotional reactivity, poor arousal tolerance, difficulty controlling affect, and frequent psychiatric

comorbidities such as depression, anxiety, and borderline personality disorders. The second subgroup, characterized by emotion "overmodulation," presents with emotional avoidance, excessively controlled behavior, a tendency toward somatization, and less obvious psychiatric comorbidity.[20,21] In clinical practice, characteristics of these subgroups frequently co-exist.

Dissociation, Conversion, and Somatization, and Their Role in PNES

Dissociation has been suggested as a major underlying mechanism in the development of PNES and refers to the disruption of the normal, subjective integration of one or more aspects of psychological or cognitive functioning. Conversion is conceptualized by some authors as a "somatoform" subtype of dissociation and refers to psychological distress being unconsciously converted into a neurological deficit whereas somatization bypasses neurocognitive processing directly into a somatic complaint.[13] Personality assessment tools identify elevations in scales that signal significant somatic complaints in PNES.[20]

Further understanding of these underlying mechanisms can help not only the development of treatment strategies aimed at the underlying presumed cause of the illness but also identification of how these traits interfere with patient's engagement and collaboration in treatment. Furthermore, a clearer explanatory model enhances the medical community's acceptance of PNES as a legitimate disorder.

NEUROMEDICAL FACTORS

Co-existing Epileptic Seizures

Between 10% and 30% of patients diagnosed with PNES also have had epileptic seizures in the past or have active co-existing epileptic seizures.[7,15] The patient and the witnesses are often able to describe a distinct semiology that differentiates a type of spell from the other. Video EEG evaluation is necessary to make the diagnosis of the 2 conditions independently. It is imperative to clearly communicate the co-existence of 2 different kinds of events to the patient, and to emphasize that they are different in etiology and presentation and require different treatment strategies.

Traumatic Brain Injury

Recent studies found a stronger association between mild traumatic brain injury (TBI) (defined as a report of loss of consciousness lasting less than 30 min or amnesia lasting less than 24 h following head trauma) and PNES than between mild TBI and epileptic seizures.[24] Mild TBI was also associated with higher incidence of depression, anxiety, and posttraumatic stress disorder in PNES. Therefore, a history of mild TBI should not sway the clinician toward considering seizures more likely to be epileptic in origin. Much to the contrary, a mild TBI may be a predictor for worse quality of life and poor outcome in PNES.

Chronic Pain

Fibromyalgia, chronic pain, and opioid medication use are more frequent in patients with PNES as compared with patients with epileptic seizures. All 3 have a high positive predictive value for a diagnosis of PNES among patients with refractory seizures.[25]

Intellectual Disability

A broad range of full-scale intelligence quotients has been reported in PNES subjects. Individuals with low IQ or learning disabilities represent a unique subpopulation of patients with PNES, where immediate circumstantial triggers are more common.[20]

Other Factors

Other comorbid conditions, proposed to be predictors of the diagnosis of PNES, include the report of multiple allergies, which could be a surrogate for the co-existence of immune-mediated mechanisms or a marker for psychopathology.[26]

NEUROPSYCHOLOGICAL DEFICITS AND COGNITIVE MODELS

Cognitive complaints are common in PNES. The neuropsychological literature has demonstrated that individuals with PNES perform outside normal limits on objective cognitive measures and an alteration in

attention regulation is perhaps the most reliable finding.[20] Although attention impairments are thought to play the main role in general cognitive deficits in PNES, they are often considered "non-specific" because they may merely represent a network disruption common to many psychiatric and neurologic conditions.

There is compelling evidence to suggest that patients with PNES demonstrate a pattern of heightened vigilance or a diminished ability to filter out irrelevant sensory stimuli when compared with individuals with epilepsy. High-order attention and executive functioning impairments may be responsible for other patterns of dysfunction in PNES, including those in verbal memory and verbal fluency.[20]

As for performance validity, failure rates in PNES are generally reported to be at 28% or higher, compared with 8% in individuals with epilepsy and the general medical population. However, malingering is not considered the main source of variability in performance validity findings in these patients. Instead, internal factors not necessarily under volitional control (i.e., tendency to avoid emotional conflict, psychiatric severity, and level of distress) as well as dysregulated control of attentional resources may be playing a role.[20]

The utility and specificity of the clinical neuropsychological evaluation in PNES are conditionally based on how systematically both cognitive and emotional/behavioral profiles are accounted for, as well as integrated. Dual cognitive-emotion paradigms, which measure performance within traditional cognitive domains (e.g., attention, executive functioning, and memory) under conditions of simultaneous emotion processing, have demonstrated reliable deficits in patients with PNES across a number of paradigms. Specifically, individuals with PNES have been reported to show attentional biases to social threat, reduced cognitive flexibility under simultaneous emotion processing conditions, and impaired working memory under an emotional distracter condition.[20] Although these dual cognitive-emotion tasks are currently relegated to more research-oriented investigations, they seem well suited to capture aberrant cognitive-emotion integration.

NEUROBIOLOGICAL MODELS

Quantitative structural and functional neuroimaging studies in PNES may provide a brain-based model for this neuropsychiatric disorder. Currently, these studies are limited to 9 published works, summarized in Table 2. Although the table enumerates a number of studies that highlight altered involvement in specific brain areas, there is not yet a conclusive unifying finding common to all studies. Findings include reductions in gray matter volumes in brain regions involved in emotion processing and motor control,[27] and altered functional connectivity among numerous areas, including those involved in motor function, emotion regulation, and cognitive control.[28,29] Altered structural white matter connectivity has also been documented in different brain regions and to differ between hemispheres.[30,31] The widespread altered connectivity in PNES suggests poor efficiency in neural coordination.[32–34] Decreased metabolism in specific regions may underlie emotion dysregulation (anterior cingulate hypometabolism) and dysfunctional processes involving self- and environmental awareness (right parietal hypometabolism).[35]

Despite some limitations, these studies suggest that PNES subjects show structural and functional alterations in brain networks that mediate various aspects of emotion processing, perceptual awareness, cognitive control, and motor behavior.

THE ROLE OF THE MULTIDISCIPLINARY TEAM

Neurologists and mental health professionals should be part of the multidisciplinary team that presents the results of the diagnostic investigations and constructs the treatment plan. In patients in whom PNES is suspected, evaluation by a mental health professional before the diagnosis is confirmed can facilitate crafting an explanatory model for the psychogenic etiology of the events. After the diagnosis is confirmed and presented, the presence of a neurologist in the treatment team assures that the possibility of co-existing epilepsy is addressed and treated, other neurological disorders are recognized, and unnecessary aggressive treatments and iatrogenic complications are avoided.

The communication of the diagnosis is a therapeutic opportunity to provide psychoeducation about the nature of the disorder, reinforce engagement in treatment, and foster an effective interaction with the health care system. When feasible, the neurologist and the mental health professional should jointly present the diagnosis. Different communication protocols have been proposed on how the

TABLE 2. Neuroimaging Studies in PNES

Study	Methodology	Subject groups	Findings in PNES subjects (compared to controls)
Labate et al.[27]	Voxel-based morphometry Cortical thickness study	PNES ($n = 20$, all with motor phenomena) Healthy controls ($n = 40$)	Reduced gray matter volmes in ACC, SMA, right middle frontal gyrus, bilateral precentral and postcentral gyrus, bilateral cerebellum. Cortical thinning in right precentral gyrus, right superior frontal gyrus, right precuneus, and right paracentral gyrus. Negative correlation between depression severity and gray matter volume in right precentral gyrus and depression severity and thickness of right OFC, right superior frontal gyrus and right paracentral gyrus.
van der Kruijs et al.[28]	Picture encoding task and Stroop task Resting state fMRI functional connectivity	PNES ($n = 11$, no psychiatric comorbidities) Healthy controls ($n = 12$)	Increased functional connectivity between the left precentral sulcus, and both the anterior insula and ACC Increased functional connectivity between the inferior frontal gyrus and both the insula and ACC. No difference in activation during cognitive tasks between groups. Positive correlation between dissociation scores and precentral sulcus and posterior insula connectivity.
Van der Kruijs et al.[29]	Resting state fMRI functional connectivity Independent component analysis of functional networks	PNES ($n = 21$, no psychiatric comorbidities) Healthy controls ($n = 27$)	Increased subgenual ACC, OFC, and insula co-activations with frontoparietal network. Increased ACC and insula co-activation with executive control network. Increased cingulate gyrus, superior parietal lobule, pre- and post-central gyri, and SMA co-activations with the sensorimotor network. Increased precuneus and cingulate gyrus co-activations with DMN. Decreased OFC co-activation executive control network. Decreased precuneus co-activation with sensorimotor network.
Ding et al.[32]	Resting state fMRI DTI Graph theoretical analysis	PNES ($n = 17$, no psychiatric comorbidities) Healthy subjects ($n = 20$)	Altered small-worldness in functional and structural organization pattern (more regular, lattice-like) in emotional control, attentional, sensorimotor, subcortical, and default mode networks. Decreased coupling of functional and structural connectivity.
Ding et al.[33]	Resting state functional connectivity density mapping	PNES ($n = 18$, no psychiatric comorbidities) Healthy subjects ($n = 20$)	Increased short-range connections in left superior and middle frontal gyri, left ACC and bilateral middle cingulate gyri. Increased long-range connections in bilateral SMA, visual processing regions, right posterior insula, right superior temporal gyrus, right pre- and post-central gyri, and left paracentral lobule. Decreases in long-range connections in right OFC, right ventrolateral prefrontal cortices and right inferior parietal lobule.
Arthuis et al.[35]	Resting state ^{18}FDG-PET	PNES ($n = 16$, no psychiatric comorbidities) Healthy controls ($n = 16$)	Hypometabolism in right inferior parietal and central region, bilateral ACC. Increased metabolic correlation between right inferior parietal/central region and bilateral cerebellum, and between bilateral ACC and left parahippocampal gyrus.
Hernando et al.[30]	DTI and tractography	PNES ($n = 8$) Healthy controls ($n = 8$)	Greater number of UF steamlines in right compared to left hemisphere within PNES group, but no interhemispheric difference within the control group. No difference in overall structural connectivity in UF between groups. Structural connectivity in UF correlated negatively with age of onset in PNES group.

Li et al.[34]	Resting state fMRI Fractional amplitude of low frequency fluctuations Functional connectivity	PNES (n = 18, no psychiatric comorbidities) Health controls (n = 20)	Increased low frequency fluctuations in the DLPFC, parietal cortices, and motor areas, decreased low frequency fluctuations in the triangular inferior frontal gyrus. Increased and decreased widespread interregional connectivity. Functional connectivity between SMA and ACC correlated positively with event frequency in PNES group.
Lee et al.[31]	DTI	PNES (n = 16) Healthy controls (n = 16)	Increased structural connectivity in left corona radiata, left internal and external capsules, left superior temporal gyrus, and left UF.

ACC = anterior cingulate cortex; DLPFC = dorsolateral prefrontal cortex; DMN = default mode network; DTI = diffusion tensor imaging; OFC = orbitofrontal cortex; fMRI = functional magnetic resonance imaging; FDG-PET = fluorodeoxyglucose–positron emission tomography; SMA = supplementary motor area; UF = uncinate fasciculus.

diagnosis of PNES should be delivered.[36] An integrated version is presented in Table 3. For a subset of patients with PNES, awareness that their events are psychogenic may prove therapeutic in itself with a remission rate close to 40% at 6–12 months in a study.[37] Reduction in health care use has also been documented after diagnosis delivery, and is maintained at 24 months.[38,39] However, the potential influence of psychological interventions initiated after diagnosis is not specified in these studies.[38,39]

Communication protocols have yet to be evaluated in relation to their efficacy at retaining patients in psychological treatment. Motivational interviewing has been evaluated in many medical diagnoses and it has shown efficacy at reducing ambivalence about treatment and facilitating behavioral change in favor of one's health.[40] Use of motivational interviewing skills may become a useful tool to help those patients who recurrently present to new providers despite previous findings documenting PNES.

A study particularly pointed out that neurologists, more so than patients, have a polarizing view of PNES as a purely psychological disorder, although patients think about it as a partly physical and partly psychological problem.[41] This discrepancy may generate different treatment expectations between patients and their neurologists and requires close attention to communication patterns. It is possible that a comprehensive, biopsychosocial explanation of the disorder would be more acceptable to patients, allowing engagement and participation in treatment.

EVIDENCE-BASED TREATMENTS

Psychotherapeutic Interventions

Although there is a general consensus that psychotherapy is the indicated form of treatment of PNES, the effectiveness of most psychotherapy modalities remains understudied.

Cognitive-behavioral therapy (CBT) is currently the most rigorously studied treatment modality and has been reported to have the highest level of efficacy evidence. Individual CBT was evaluated in a randomized controlled trial that compared CBT to standard medical care with a significant reduction in monthly event frequency after 12 sessions.[42] The active group received CBT in which the following concepts were addressed: (1) treatment engagement, (2) reinforcement of independence, (3) distraction, relaxation, and

TABLE 3. Diagnosis Delivery: Communication Protocol

Covered topic	Communication points delivered to patient
Negative diagnosis	What you don't have (i.e., epilepsy) What you don't need (i.e., treatment with antiepileptic drugs)—unless needed for other indications
Diagnostic method	How the diagnosis was made (i.e., video-EEG captured typical event) "It is common!," frequently seen in long-term monitoring units
Genuine symptoms	Symptoms are real, not fabricated
Explanatory model (positive diagnosis)	Role of accumulating risk factors over time and automatic functional brain patterns
Suggestion	Some patients improve with reassurance that their events are not epileptic and once the diagnosis is explained
Treatment and expectations	There are effective treatments Psychotherapy works though skills learning, "brain re-training" There is no sudden cure, treatment requires time and training

refocusing techniques when episode is imminent, (4) graded exposure to avoided situations, (5) cognitive restructuring, and (6) relapse prevention. A multicenter pilot randomized study that produced class I data randomized 34 patients into 1 of 4 treatment arms: (1) flexible-dose sertraline hydrochloride only ($n = 9$), (2) CBT−informed psychotherapy (based on a treatment manual currently available),[43,44] (3) CBT-informed psychotherapy with sertraline, and (4) treatment as usual. The CBT-informed psychotherapy and CBT-informed psychotherapy plus sertraline showed significant improvements in monthly event reduction.[45] Other uncontrolled studies have evaluated the efficacy of CBT in an outpatient,[46] and an inpatient setting,[47] with positive results. Psychoeducation, relaxation training, exposure to avoided situations, and cognitive restructuring are common techniques used in CBT. A self-guided help based on a CBT approach was successful at reducing various functional neurological symptoms, including PNES, based on a controlled study.[48] Similarly, group CBT was examined in an uncontrolled study, in patients with functional neurological symptoms, some of which had PNES.[49] Empirically-validated PTSD-specific CBT methods, such as prolonged exposure therapy,[50] are now being considered in dually-diagnosed patients with PNES/PTSD and are showing promising early results.[51]

Psychodynamic psychotherapy has not been as rigorously examined as CBT, but favorable results have been demonstrated in uncontrolled studies using individual and group formats.[52–54] From the psychodynamic perspective, psychogenic symptoms are produced by internal processes resulting from early traumatic memories that are maintained at an unconscious level through dissociative and somatic defense mechanisms. The goal of psychodynamic psychotherapy is to bring unconscious material to the surface to promote change through insight.

Mindfulness techniques help challenge experiential avoidance while delineating personal values. In a case series that used a mindfulness-based treatment protocol, event reduction was demonstrated using this approach.[55] Hypnotherapy was investigated in patients with FNSD, which included PNES, in 2 controlled studies.[56,57] One of these 2 studies, the one that compared hypnotherapy against a wait list control group showed favorable results for the active intervention.[57]

Psychoeducational group interventions are particularly attractive because they can be administered by a wide range of professionals and are generally inexpensive. A recent controlled psychoeducational intervention showed functional improvement, but no change in event frequency.[58] Earlier uncontrolled psychoeducational interventions have reported decreases in posttraumatic and dissociative symptoms and emotionally-based coping mechanisms[59] and a decline in event frequency.[60,61] Group psychotherapy that uses a variety of approaches (psychoeducation, behavioral therapy, and psychoanalytic therapy) have shown symptomatic improvement in an uncontrolled study.[62]

Psychopharmacologic Interventions

Pharmacologic treatment in PNES may target psychiatric comorbidities or the functional neurological

disorder itself. To date, there are 4 prospective studies that evaluated the efficacy of psychopharmacologic agents in PNES. A double-blind, placebo-controlled study showed no difference in event frequency between flexible-dose sertraline and placebo.[63] As one of the arms in the multicenter study cited earlier,[34] the medication-only arm (sertraline) did not show a significant within-arm reduction in event frequency at the end of the study. A controlled study compared diazepam to inpatient paradoxical intention, where the medication arm fared worse than the nonmedication intervention in event frequency and reduction in anxiety severity.[64] The only positive psychopharmacologic study is an uncontrolled trial of venlafaxine that demonstrated improvement in event frequency at 5 months.[65] Of note, none of the mentioned studies that evaluated the effectiveness of antidepressants in PNES excluded patients with other antidepressant-responsive conditions, such as depressive or anxiety disorders. As a matter of fact, the uncontrolled trial that evaluated the effectiveness of venlafaxine in PNES required that enrolled subjects met criteria for a depressive disorder or generalized anxiety disorder, whose severity also improved and was maintained throughout the course of the study.[65]

Evidence-based treatment guidelines exist for the treatment of commonly comorbid conditions, such as major depression[66] and PTSD.[67] Treatment of comorbidities should be maximized concurrently as PNES-specific treatment is provided. In this context, for instance, prazosin, an alpha-1 adrenergic antagonist, has demonstrated effectiveness in the treatment of PTSD-related nightmares and overall PTSD severity.[68] This intervention has not been studied in PNES; however, given its frequent association to trauma, control of comorbid PTSD should receive full attention as part of the overall treatment plan in patients with PNES.

Although psychopharmacologic interventions may play a role in PNES treatment, mostly to address psychiatric comorbidities, psychotherapy has consistently shown more positive results in trials. Further details on the studies cited earlier can be found in Table 4. The table divides these studies based on their level of methodologic rigor and studied population (PNES alone or mixed with other FNSDs). The reader is encouraged to consider the methodology and subjects that each study used, before focusing on the specific comments, to understand our current limitations in the level of evidence of treatments for PNES.

LONG-TERM OUTCOMES

Although there are encouraging developments in the effectiveness of short-term interventions for PNES, these have yet to be matched by equally concentrated efforts in the area of long-term maintenance and outcomes. The inherently heterogeneous and complex nature of PNES suggests that this disorder may well be a lifelong condition that requires continued support and treatment revisions over time. Studies on long-term results have primarily focused on reduction of event frequency and functional status.

Long-term outcome studies in PNES vary significantly in time frame and method of evaluation. Continuing symptoms range from 26% at 5–10 years to 71% at 1–10 years after the diagnosis.[69]

Improvements in event frequency are not necessarily accompanied by improvements in functional status with the latter either being much smaller or negligible compared with symptomatic recovery. A study demonstrated that "economically active" patients at baseline were 5 times more likely to become event free.[52]

The rate of newly developed somatic complaints has ranged between 6% and 25% in the 6–12-month period after diagnosis.[70,71] This is an indication that even when PNES improve, the underlying psychopathology may remain active.

Baseline predictors of poor outcome include comorbid epilepsy, various psychiatric diagnoses, violent motor semiology, high emergency department use, and receiving social security benefits.[69,72] Better outcome was found in those with higher education, younger age of onset and diagnosis, acceptance of the diagnosis, antecedent bullying, shorter duration of illness, good social support, employment at baseline, and lower somatization and depersonalization scores.[69,72]

It is clear that a significant proportion of patients continue to experience events many years after the diagnosis. Even more alarming, a significant proportion of patients remain disabled. These data call for the development of treatment strategies that take into account patients with PNES who remain disabled and possibly symptomatic on a chronic basis. Although many patients may experience PNES symptom alleviation, disability from other psychiatric or somatic symptom disorders may drive the high rates of unemployment and dependence on social security benefits that persist over time. Hence, a broad-disorder spectrum and individually tailored

TABLE 4. Evidence-Based Treatment Interventions for PNES

Study	*N*	Intervention/s	Design	Outcome
Randomized controlled trials in patients with PNES				
LaFrance et al.[45]	34	CBT-informed psychotherapy (CBT-ip, 12 sessions) vs sertraline vs CBT-ip + sertraline vs treatment-as-usual	Randomized	Within-group analysis showed significant decline in event frequency in CBT-ip and CBT-ip + sertraline groups, but not in the other groups. Improvement in many secondary measures in both CBT-ip arms. No comparison between groups.
Chen et al.[58]	34	Psychoeducational meetings (monthly, 3 times) vs routine seizure clinic	Randomized	No significant differences in event frequency between groups at treatment end or at 3-mo follow-up. Significant improvement in work and social adjustment scale in intervention (psychoeducation) group. Trend toward decreased medical use in intervention group.
Goldstein et al.[42]	66	CBT (12 sessions) + standard medical care (SMC) vs SMC alone	Randomized	Significant lower event frequency in CBT group at treatment end; significance lost at 6-mo follow-up. Mood and employment status showed no change. Both groups with decrease in medical use.
LaFrance et al.[63]	33	Sertraline 25–200 mg/d vs placebo for 12 wk	Randomized, double-blind, placebo-controlled	No difference in event frequency between groups. No difference in secondary measures. Relative change in within-group event frequency (45% decline in event frequency in sertraline group vs 8% increase in placebo group).
Ataoglu et al.[65]	30	Paradoxical intention (inpatient, 3 wk) vs diazepam (outpatient, 6 wk)	Randomized	Trend toward significantly higher percentage of patients with event freedom in last 2 wk in the paradoxical intention group.
Randomized controlled trials in patients with functional neurological symptom disorder (including a subset of patients with PNES)				
Sharpe et al.[48]	125 (12 with PNES)	CBT-p (plus maximum 4 30-min guidance sessions) + SMC vs SMC	Randomized	Overall health, functional neurological symptoms and symptom burden improved further in intervention group at 3 mo. Functional neurological symptoms improvement maintained at 6 mo, plus anxiety and physical function improvement at 6 mo.
Moene et al.[56]	44 (2 with PNES)	Weekly hypnosis sessions (10 wk) vs wait list (3 mo)	Randomized	Significant improvement in functional neurological symptoms and level of impairment in the hypnosis arm at treatment end and at 6-mo follow-up. No improvement in psychopathology.
Moene et al[57]	45 (8 with PNES)	Inpatient hypnosis (8 sessions) vs inpatient admission without hypnosis (both groups for 12 wk)	Randomized	Hypnosis did not provide additional benefit. Both groups showed improvement in functional neurological symptoms at treatment end and at 6-month follow-up. Improvement in psychopathology not specific to intervention group.
Uncontrolled trials and case series of patients with PNES				
Conwill et al.[49]	10 (+6 with other FNS)	Group CBT (weekly for 4 wk)	Uncontrolled	Non-significant improvement in event frequency (for PNES subjects only). Improvement in emotional well-being and role limitation due to emotional well-being in entire group (for PNES + other FNS subjects).
Baslet et al.[55]	6	Mindfulness-based psychotherapy (12 sessions completed in 15–43 wk)	Case series, uncontrolled	All patients experienced reduction in weekly event frequency, with 3 of the 6 achieving event remission by treatment end. Reduction in depression and anxiety measures.

TABLE 4. Continued

Study	*N*	Intervention/s	Design	Outcome
Santos Nde et al.[53]	37	Psychoanalytic psychotherapy (weekly for 12 mo)	Uncontrolled	Event remission in 29.7% of patients (10% remission in completers) and reduction in frequency in 51.4% of patients. Decrease in health care use.
Mayor et al.[61]	20	Brief individual psychoeducational intervention (4 sessions)	Uncontrolled	A total of 4 of 13 completers were event free, and an additional 3 completers reported >50% improvement in event frequency, approximately 7 mo after diagnosis. When whole group analyzed, no difference in event frequency pre- and post- intervention.
Metin et al.[62]	9	"Eclectic" group psychotherapy (weekly for 12 wk)	Uncontrolled	Significant reduction in event frequency at end of treatment and at 12-mo follow-up. Significant improvement in quality of life (mental health) and state and trait anxiety at end of treatment. No improvement in depression, dissociation, or alexithymia.
Mayor et al.[52]	47	Brief augmented psychodynamic interpersonal psychotherapy (1–18 sessions, median of 5 sessions, at weekly or biweekly frequency)	Retrospective, uncontrolled	Significant reduction in event frequency at follow-up (median, 42 mo after end of treatment). At follow-up, 25.5% of patients had become event free. A further 40.4% had event reduction of >50%. Health care use declined significantly from baseline to follow-up.
Pintor et al.[65]	19	Venlafaxine 75–300 mg/d for 5 mo	Open-label, uncontrolled	Significant reduction in event frequency by treatment end. Significant improvement in anxiety and depression measures.
LaFrance et al.[46]	17	CBT (weekly for 12 wk)	Uncontrolled	Significant reduction in weekly event frequency at treatment end. Improvement in most secondary measures including depression, trauma symptoms, impulsivity, overall psychopathology, and quality of life.
Kuyk et al.[47]	22	Multimodal CBT-informed individualized inpatient treatment for 2-6 mo	Uncontrolled	Significant decrease in weekly event frequency from baseline to discharge, and then at 6-mo follow-up. Significant improvement in all secondary measures (depression, dissociation, overall psychopathology, and quality of life) from baseline to 6-mo follow-up.
Barry et al.[54]	7	Group psychodynamic psychotherapy (weekly for 32 wk)	Uncontrolled	Six of 7 patients with decrease in event frequency over course of treatment; 4 of 7 with event remission. A total of 5 patients remained event free several months after treatment. Improvement in depression and overall psychopathology.
Zaroff et al.[59]	7	Group psychoeducational intervention (weekly for 10 wk)	Uncontrolled	A total of 3 patients achieved remission at treatment initiation. Four subjects with no change in event frequency, 2 with decrease, and 1 with increase. When whole group analyzed, no difference in event frequency between pre- and post-intervention. Improvement in trauma symptoms, anger expression and quality of life.
Prigatano et al.[60]	15	Group psychoeducational intervention (weekly for 6 mo —24 sessions)	Uncontrolled	A total of 6 out of 9 completers with decrease in event frequency, 2 with no change and 1 with increase, when comparing the first 12 sessions with the 12 last sessions.

CBT = cognitive-behavioral therapy; CBT-ip = CBT-informed psychotherapy; SMC = standard medical care; FNS = functional neurologic symptoms; wk = weeks; mo = months; mg/d = mg per day.

TABLE 5. Common Challenges in the Treatment of PNES

Patient-dependent factors		Recommended action
Acceptance of diagnosis	Patient does not accept diagnosis	Provide a follow-up appointment to continue discussion Allow patient to verbalize doubts Provide mind-body explanatory models
	Patient accepts diagnosis	Streamline referral to treatment
Avoidance tendencies	Patient with high avoidance	Create alliance with avoidant tendencies by presenting treatment as collaborative rather than challenging
	Patient is less avoidant	Present patient with clear treatment rationale of standard treatments
Locus of control	External	Engage patient actively in their treatment (i.e., keeping logs, practicing relaxation exercises and assessing changes)
Symptom migration		Provide unitary explanatory model that addresses all psychogenic symptoms
Disability benefits	Patient is seeking disability benefits	If possible, postpone application until treatment has ended
	Patient already qualified as disabled	Examine motivation to improve and develop goals
Social isolation	Patient has a social network	Engage available social resources
	Patient is socially isolated	Engage patient in community activities (i.e., support group, clinic-based wellness activities) to increase social contact
Provider-dependent factors		
Mental health professionals lack knowledge about PNES		Professional education about PNES should be provided in training programs and through continuing education
Suspicion of malingering		Education on the etiology of the disorder and therapeutic evaluation of motivation
Liability and practical concerns regarding events in office	Risk of injury	Make appropriate accommodations (e.g., carpeting, padding on furniture, have patient sit on floor)
	Continue session when episode occurs during session?	If patient recovers, session may often continue
	Patient is incapacitated by prolonged event	Patient must come accompanied by someone who can safely transport her/him back home
Systems-based factors		
Limited number of mental health clinicians who accept health insurance		Mental health parity Widespread training
Gaps in treatment transition		Establish emergency protocols. If possible, avoid long waits before first treatment appointment, follow-up by referring clinician Interdisciplinary collaboration
Fragmented care		If possible, provide care in same facility as where diagnosis was made Interdisciplinary collaboration

approach that targets many of these conditions is necessary to optimize long-term functioning in this population.

CHALLENGES IN THE MANAGEMENT OF PNES

Failure to follow up on treatment recommendations represents a serious challenge in PNES with up to 30% of patients failing to comply with an initial referral to mental health treatment.[71] Patient-dependent factors that make treatment of PNES challenging include patients not accepting the diagnosis,[73] avoiding discussion of distressing topics, having an external health locus of control,[74] development of new somatic symptoms (called symptom replacement or migration),[70] social isolation and identifying with the "disabled" role.[71] Some of these factors are intrinsic to the patient's own psychopathology. Future research should determine if there are subgroups within the PNES population for which tailored treatments would be more effective than a common treatment of all subgroups. These tailored approaches should consider the identification of underlying traits (such as alexithymia, fear sensitivity, dissociative tendencies, emotion regulation style) as clearly identifiable and measurable targets for treatment, including engagement in treatment. Provider-dependent factors also

contribute to making treatment of PNES challenging, and these include lack of clarity as to whether neurologists or psychiatrists are responsible for the treatment of the patient,[75] lack of formal training, liability concerns, and questioning the diagnosis or the volitional nature of symptoms.[76,77]

Finally, systems-based factors also play a role in the difficulty some providers encounter. Gaps in treatment transition among emergency departments, epilepsy specialists, and mental health professionals, fragmented care, lack of interdisciplinary collaboration, and limited number of clinicians who are adept to treat the condition and would accept patient's insurance are just some of the systems-based challenges.

Table 5 lists these challenges in more detail and provides some concrete tips on how these may be tackled to enhance treatment participation and success. It is unlikely that outcomes for patients would improve if interdisciplinary collaboration remains absent. Neurologists must understand that they are necessary participants because of their vital role in making the diagnosis, communicating it adequately, and transitioning patients to treatment, whereas mental health professionals are just as intrinsically involved because of the psychogenic nature of this condition along with potential comorbidities that require intensive and sometimes lifelong psychiatric treatment. Addressing all these factors is essential, and our role as treatment providers at helping other colleagues understand this condition cannot be underestimated.

CONCLUSIONS

PNES is a complex neuropsychiatric disorder. Many etiologic factors (neurobiological, cognitive, and psychosocial) create a predisposition toward and eventually precipitate and maintain the symptom. At a practical level, interdisciplinary collaboration has been highlighted as necessary to facilitate accurate diagnosis, engagement in treatment, and eventually successful outcomes. Although the literature on treatment remains limited, there is growing evidence that supports the use of psychotherapeutic interventions. A 2-page handout is provided as an appendix and is intended to help clinicians in the discussion of the diagnosis and treatment planning with patients. Encouraging future directions include considering evidence-based methods for associated disorders (e.g., prolonged exposure therapy in PTSD) to assess their effectiveness in the PNES population. When developing treatment programs for patients with PNES, long-term outcomes need to be considered. Neurologists and psychiatrists should define their interdisciplinary collaboration while jointly taking responsibility for specific aspects in the care of these patients who suffer from a disorder that is disabling and commonly chronic.

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