



# Seizures, Nonepileptic Events, Trauma, Anxiety, or All of the Above

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## Psychiatric Comorbidity and Traumatic Brain Injury Attribution in Patients With Psychogenic Nonepileptic or Epileptic Seizures: A Multicenter Study of US Veterans

Salinsky M, Rutecki P, Parko K, Goy E, Storzbach D, O'Neil M, Binder L, Joos S. *Epilepsia*. 2018. Epub ahead of print. <https://doi.org/10.1111/epi.14542>

**Objective:** To determine the frequency and severity of psychiatric disorders and attribution of seizures to traumatic brain injury (TBI) in veterans with verified psychogenic nonepileptic seizures (PNES) versus epileptic seizures (ES). **Methods:** We studied 333 consecutive admissions to the monitoring units of 3 Veterans Administration epilepsy centers. All patients underwent continuous video-electroencephalographic recording to define definite PNES or ES. Evaluations included the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 4th edition, posttraumatic stress disorder (PTSD) Checklist, Beck Depression Inventory II, and Patient Seizure Etiology Questionnaire. Interviews and questionnaires were completed prior to final seizure type diagnosis and patient debriefing. The primary outcome measure was a comparison of Axis I psychiatric diagnoses in patients diagnosed with PNES versus ES. **Results:** A total of 81 patients were diagnosed with PNES and 70 with ES. Posttraumatic stress disorder was the most frequent Axis I diagnosis in veterans with PNES (64% vs 13% of those with ES;  $P < .001$ ). Posttraumatic stress disorder was common regardless of deployment to a war theater or combat exposure. Mood, substance abuse, and anxiety disorders were also more common in the PNES group. Traumatic brain injury was cited as a likely cause of seizures by 47% of veterans with PNES versus 25% of those with ES ( $P = .01$ ). Posttraumatic stress disorder and attribution of seizures to TBI were found in 30% of veterans with PNES versus 3% of those with ES ( $P < .001$ ). **Significance:** In veterans referred for inpatient seizure evaluation, PTSD was strongly associated with a diagnosis of PNES versus ES. The association of PNES with PTSD, attribution of seizures to TBI, or both, may prompt early consideration of PNES.

## Commentary

The association of epilepsy and anxiety continues to be frequently observed and confirmed.<sup>1</sup> However, oddly enough, the association of psychogenic nonepileptic seizures (PNES) and anxiety has been less well established. It is intuitive to consider that anxiety may lead to PNES, though this is a difficult point to prove because anxiety itself is heterogeneous. It may still be inadequate to say that anxiety disorders are uniformly present in PNES, and even more speculative to claim causality, even though the intuition for such association is quite strong.

Salinsky et al have brought us much closer to answer this etiologic question. The population studied encompasses veterans, clearly a group that is forced to confront anxiety. Prospectively enrolled patients with questionable paroxysms underwent observation on an inpatient epilepsy monitoring unit in order to assess whether PNES or electrical seizures were present. Impressively, a solid psychiatric assessment was done

for each patient, including a structured diagnostic interview, the gold standard for diagnosing psychiatric conditions. For corroboration, the investigators also used well-established questionnaires to verify the presence of posttraumatic stress disorder (*Diagnostic and Statistical Manual of Mental Disorders [Fourth Edition]*) and other anxiety symptoms. The Beck depression scale and posttraumatic stress disorder (PTSD) scales are useful tools, and regardless of any other shortcomings of the study, the authors deserve credit for thinking to use such assessment tools prospectively.

The results show that PTSD is more common in those with PNES and that patients with PNES attribute their symptoms to a head injury more often than do those with electrical seizures. Additionally, psychiatric illness, particularly mood and anxiety disorders, were more often present in those with PNES than those with epilepsy. The investigators performed the psychiatric evaluations prior to the epilepsy monitoring, which effectively reduces bias of the findings.



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The results are intriguing and may offer tangible evidence of the relationship between anxiety, and epilepsy, and PNES. Simply finding such clear relationships is notable and important. Characterization of psychiatric illness in epilepsy as well as in PNES has been challenging for many years, despite persisting clinical suspicions. Some groups have found reasonable associations of psychiatric illness with PNES,<sup>2,3</sup> but subgroups with marked exposure to stress, such as veterans, have been infrequently studied even though they may be a higher yield population with which to find such an association.

Investigating the possible high yield was an aim of a study by Moshe et al, which found that exposure to combat increased the likelihood of developing epilepsy, presumably by means of the increased exposure to anxiety provoking events.<sup>4</sup> The idea that stress could lead to the development of epilepsy is a critical observation and challenges classical paradigms of epilepsy etiology.

Yet, in this study, the exposure to combat was equally associated with epilepsy or with PNES, so it augments rather than replicates the findings of Moshe et al. Even though PNES is overrepresented in military populations, combat did not increase its presence. The fact that exposure to combat did not predict either epilepsy or PNES is in accordance with what we know about PTSD. Either actual threat or perceived threat rate equally in the development of PTSD symptoms. Even though some soldiers did not experience combat, the very possibility of a calamitous outcome appeared to lead to a PTSD diagnoses just as often.

The attribution that patients make regarding their events is also interesting. Patients with PNES were more likely to consider that a head injury was at fault for their difficulties. The fact that patients with electrical seizures did not make such an attribution is perhaps meaningful in that a person with PTSD will commonly seek explanations for their ambiguous or amorphous symptoms. Posttraumatic stress disorder has nonspecific physiologic components that include heart rate elevations, hyper states of alertness, and exaggerated startle responses, all of which may compel explanatory speculation and conjecture in the absence of clear neurophysiologic causes.

While the association between psychiatric illness and PNES is strong, the association between psychiatric illness and epilepsy is also quite significant. It is remarkable that depression or anxiety was present in nearly 40% of those with epilepsy and without PNES. Any Axis I psychiatric illness was found in 57% of the sample with epilepsy, also a notable finding, even compared to the 94% of the comorbidity found in the PNES group.

Despite these robust associations, there are difficulties in drawing conclusions, given some critical methodologic issues. It is simply untenable to consider that only 7 of the 460 individuals in the sample had a combination of PNES and epilepsy. Clinically, it has been long suspected that the most common comorbidity of the patient with PNES is epilepsy.<sup>5,6</sup> The other

major problem is that the largest portion of the sample, 153 (33%) of the 460 was deemed to have an inconclusive EEG. It seems particularly odd that even with extended monitoring, one third of the sample had no clear explanation one way or the other for their paroxysmal events. That fact itself may be exquisitely informative, and given that this is the largest subgroup of the sample, further information and characterization seems necessary. The authors have not provided that information and apparently the reviewers and editors of the journal did not request it. As a result, meaningful conclusions about the true role of anxiety or trauma in epilepsy or in PNES from this data set are tentative.

In any case, the authors deserve praise for doing this study and offering at least a possible correlate between anxiety in its extreme form, PTSD, and PNES. That itself is a valuable contribution and will help practitioners focus efforts for diagnosis and treatment. The open questions regarding the few patients with a proven combination of events or the sizeable plurality that could not be characterized will have to wait for the next study.

By Jay Salpekar

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