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Assessing the hidden burden of psychiatric disease in patients with non epileptic seizures

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ABSTRACT

Nonepileptic seizures are commonly associated with psychiatric comorbidities, and specifically PTSD. Despite increased prevalence of psychiatric disease noted on referral of patients to our dedicated clinic for nonepileptic seizures, we found even higher rates of comorbid psychiatric disease or significant symptomatology after our initial clinic intakes, whereby patients are formally evaluated by a behavioral health provider, in addition to an epileptologist. After intake, an additional 21% of patients were identified as having PTSD or significant trauma-related symptoms, an additional 7% of patients were identified with significant anxiety or panic-related symptoms, and an additional 11% of patients were identified with significant depressive symptoms. While highly effective treatment of nonepileptic seizures remains elusive, well-developed treatment paradigms with proven efficacy exist for depression, anxiety, and PTSD. Eliciting these psychiatric comorbidities and pursuing targeted treatments, especially for those patients that do not have easy access to providers with dedicated expertise in the management of nonepileptic seizures, may be a more easily scalable and implementable treatment modality for these patients.

1. Introduction

Nonepileptic seizures (psychogenic nonepileptic seizures, dissociative seizures, functional seizures) are paroxysmal events during which patients lose voluntary control of motor, sensory, or cognitive function that can appear similar to a variety of other physiological phenomena but are frequently difficult to distinguish from epileptic seizures. These diagnostic dilemmas are often encountered by emergency room staff, in the neurologists' clinics, and as referrals to dedicated epilepsy centers [1,2]. After arriving at the correct diagnosis, effective treatment remains elusive. While the etiology of nonepileptic seizures (NES) at the level of the underlying neurophysiological mechanisms is poorly understood, psychiatric comorbidities and especially a history of psychological trauma are frequently observed among these patients [3,4]. These observations have led to the long-held theory that NES are a conversion disorder or some other manifestation of psychiatric disease and hence the name "psychogenic" nonepileptic seizures [5]. Psychiatric disease does not tell the whole story as chronic medical conditions including asthma and chronic pain as well as TBI have been linked to NES. Additionally, a small percentage of patients with NES do not have any psychiatric comorbidities [4,6–8]. Reflecting these observations, the DSM-V no longer requires a psychological cause to make the diagnosis of NES, as well as the broader categories of conversion disorder and functional neurological disorders [9].

Based on these historical observations, treatment attempts for NES have borrowed heavily from psychiatry [10,11]. Nonepileptic seizure-specific cognitive behavioral therapy (CBT) did not show a reduction in seizure frequency at 12 months, but did yield improvement on several secondary measures including quality of life and psychological distress in the CODES trial [12]. Sertraline may help patients with NES when used in conjunction with psychotherapy, but alone does not provide significant benefits [13,14]. One small study (19 patients) of venlafaxine in patients with NES *and* comorbid anxiety and/or depression showed potential benefits in reducing frequency of NES [15]. Our group has shown benefits with a multidisciplinary clinic implementing a 6- or 18-week group therapy model, as measured indirectly by healthcare utilization, showing that patients with NES have reduced frequency of ED visits for seizures, EMU stays, and neuroimaging studies both during and after treatment [16]. While ILAE consensus guidelines exist to guide treatment of comorbid neuropsychiatric conditions in epilepsy, as yet no guidelines exist for patients with NES [17].

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Common sense (and the evidence) suggests that outcomes related to mental health disorders are improved when treated, though our ability to effectively treat PTSD notably lags behind that of depression and anxiety [18–22]. At the NES clinic at the University of Colorado, we noticed that the patients referred for evaluation and treatment appeared to have lower prevalence of comorbid mental health disorders than expected, but that after initial intake in our clinic, these comorbidities were in fact present, either not diagnosed or not documented (and too often un- or undertreated) at the time of referral. This study aimed to better characterize how frequent psychiatric illness is documented prior to referral to our NES clinic compared to the actual rates of psychiatric illness documented (or newly diagnosed) at clinic intake. While access to multidisciplinary NES clinics or any treatment modality dedicated specifically to the treatment of NES is rare, we hypothesize that the under recognition and undertreatment of psychiatric disease in this patient population represents an important and more broadly accessible treatment option that can yield improvements in quality of life, regardless of impact on NES severity.

2. Materials and methods

This cross-sectional, chart review study was approved by the Colorado Multiple Institution Review Board (COMIRB) with a waiver for informed consent as the studied clinical information was collected as a standard of routine care for patients presenting to the neurology clinic.

Data were obtained for patients evaluated and treated in the Nonepileptic Seizures Clinic between 7/1/2016 and 2/3/2021. Note that on 3/16/2020 our clinic transitioned entirely to telehealth in light of the COVID-19 pandemic. Patient clinical data at the time of referral were obtained from the note from the referring provider, including relevant history and other clinical information available in the chart at that time and throughout this paper will be described as data available "at referral." During initial intake for the NES clinic patients are formally evaluated by a behavioral health provider (either a psychiatrist if the patient had not previously had such an evaluation or by a licensed clinical social worker if they had previously been seen by a psychiatrist), in addition to an epileptologist, during which the relevant clinical information was obtained and capture of typical nonepileptic seizure was verified. This intake process includes administering several screening scales, including the PHQ9 for depression, the GAD7 for anxiety, and the SPRINT for PTSD, among others [23–25]. As our intake process has evolved gradually since inception, patients were only included if they had completed a formal history and physical with an epileptologist and a behavioral health provider within the above-mentioned timeline and had filled out at least one of the intake screening scales (the screening scales utilized have evolved over time, but the PHQ9, GAD7, and SPRINT have been utilized with almost all referred patients). Other than inclusion of the above-described intake scales, the behavioral health evaluations were no different than the standard history and physical performed for any patient presenting with mental health concerns. The "after intake" data refer to clinical history and information available in the chart after these first intake evaluations in the clinic and were found in the behavioral health history and physical note, the screening scale forms, and the attending epileptologist's history and physical note. Between 7/1/2016 and 2/3/2021, 737 patients were referred to our NES clinic and 167 (23%) of these met the above criteria to be included in this study. All 167 patients had video-electroencephalogram (EEG) confirmed NES. 189 (26%) never established care with the clinic (unable to be contacted, no showed, or not interested in scheduling a visit), 137 (19%) patients were excluded for not completing any of the psychiatric screening scales, and another 244 (33%) patients were excluded as their evaluation and treatment otherwise varied from the standard as described above for various reasons, including those that did not complete the entire intake process (some only saw the epileptologist or the behavioral health providers) before being lost to follow-up and those whose diagnoses of NES could not be confirmed (often due to absence of available video EEG data).

Of the 167 patients included, 79 (47%) were referred from the University of Colorado Epilepsy Monitoring Unit, 48 (29%) were referred from providers within the University of Colorado system, 25 (15%) were referred from providers outside the University of Colorado system, and 12 (7%) were referred directly from the University of Colorado emergency department. Among the outside referrals, 18 patients were referred from community outpatient neurology clinics, 3 were referred from other emergency departments, 2 were referred from community behavioral health providers, and 2 were referred from their primary care provider

When considering psychiatric diagnoses, efforts were made to include all patients with documentation referring to significant psychiatric symptoms, even if the formal DSM-V diagnosis was not provided [9]. As an example, non-behavioral health trained providers often document "depression" or "anxiety" as opposed to the formal diagnoses of "major depressive disorder" or "generalized anxiety disorder." Similarly, patients were encountered with significant psychiatric symptoms that did not meet the DSM-V criteria for a diagnosis. If the symptoms were deemed significant enough to be included in documentation by our behavioral health providers after their initial clinic evaluation, we included those patients under the relevant diagnoses. For instance, our behavioral health providers denote significant symptoms when they plan to actively follow them up and/or implement treatment (even if formal diagnostic criteria are not met). Anxiety and panic symptoms (and their respective disorders) were considered together, primarily due to the difficulty to distinguish between the two in many providers' documentation, and the fact that they encompass a spectrum of similar symptoms.

Statistical analysis was performed by calculating Cohen's kappa and percent agreement as measures of inter-rater reliability to compare the "at referral" and "after intake" frequencies of each diagnosis. Chi-Square tests, Fisher's Exact test, or McNemar's tests, where relevant, were utilized for comparing the results of the screening tools between patients with and without each relevant diagnosis (the PHQ9 for depression, the GAD7 for anxiety, and the SPRINT for PTSD), as well as comparing the documented prevalence of any psychiatric comorbidity "at referral" to "after intake." Relevant "cutoff" scores are denoted in our tables for each of the screening tools and based on prior literature distinguishing mild, moderate, moderately severe, and severe depression for the PHQ9 as well as mild, moderate, and severe anxiety for the GAD7 [23,24]. The SPRINT score utilizes a single cutoff at 14 points to screen positive or negative for possible PTSD [25].

3. Results

Table 1 summarizes the patient demographics of the 167 patients included in this study. Most patients were white women, and a large majority were insured with either private insurance, Medicare, or Medicaid. Table 2 summarizes the overall prevalence of psychiatric comorbidities within this population in comparison to the total number of conditions included in a patient's chart (this includes all medical and psychiatric conditions), as well as rates of comorbid epilepsy, comparing information included in the chart at referral to that which was obtained after intake. After intake to our NES clinic, only 9% of patients did not have a formal psychiatric

Table 1
Patient demographics.

Demographics	*N* (total = 167)
Mean Age (Range)	39 (19–74)
Gender	
Female	126 (75%)
Male	39 (23%
Identify as other gender	2 (1%)
Race/Ethnicity	
White or Caucasian	120 (72%)
Black or African American	12 (7%)
American Indian and Alaskan Native	3 (2%)
Asian	2 (1%)
Other or Unknown Race	10 (6%)
Hispanic or Latino	21 (13%)
Insurance Status	
Medicaid	68 (41%)
Private Insurance	66 (40%)
Medicare	24 (14%)
VA Administration or Tricare	8 (5%)
No Insurance	1 (0.5%)

Table 2
Comparing the rates of psychiatric comorbidities relative to all comorbidities before and after clinic intake.

	At Referral	After Intake
Mean number of conditions documented	7.7	7.4
Mean number of psychiatric conditions documented	2.1	2.3
Number of patients with comorbid epilepsy	17 (8%)	17 (8%)
Number of patients with no psychiatric comorbidities	29 (17%)+	15 (9%)+

+ denotes p value <0.01 by McNemar's test.

Table 3
Scores on screening scales among patients with no documented psychiatric comorbidities.

No Psychiatric Comorbidities after intake	Mean PHQ9 (range) *N* = 13	Mean GAD7 (range) *N* = 13	Mean SPRINT (range) *N* = 15
15 (9%)	8.8 (2–14)	5.5 (1–21)	14.3 (3–24)

Mean PHQ9, GAD7, and SPRINT scores among patients with no psychiatric comorbidities after intake.

diagnosis, decreased from 17% based on referral data (Table 2), and even among those patients, the screening tests administered for depression, anxiety, and PTSD suggested significant burden of psychological symptoms, even if clinical indications for treatment were not yet apparent (Table 3).

Tables 4, 5, and 6 summarize rates of specific psychiatric comorbidities and chronic pain, substance use, and suicidality and self-injurious behavior, respectively, with comparison between data available at referral versus after intake. The number of patients for which a specific diagnosis was added or removed *after intake* are also included in these tables. PTSD, Depression, and Anxiety/Panic represented the three most common comorbidities and were not diagnosed (or at least not documented) in 21%, 7%, and 11%, respectively, at referral (Table 4). Among those referred with diagnoses of depression, anxiety/panic, or bipolar disorder, 8%, 5%, and 5%, respectively, did not meet the criteria for their diagnosis after intake (Table 4). The inter-rater reliability measured by kappa and percent agreement was lowest among PTSD and trauma-related symptoms within our population, compared to all other studied diagnoses.

Tables 7, 8, and 9 summarize data regarding screening scales administered at clinic intake, specifically to evaluate for depression, anxiety, and PTSD, using the PHQ9, GAD-7, and SPRINT scores. These tables compare the scores between patients with and without the relevant diagnosis for which each scale is screening, and clearly document that significant symptomatology is present among patients that may not meet criteria for formal diagnosis.

4. Discussion

This study highlights the prevalence as well as the underdiagnosis and misdiagnosis of psychiatric comorbidities among NES patients. These represent large numbers of patients that either have significant mental health disorders that are not being recognized and appropriately treated, or patients that are at risk of being identified and treated for the wrong conditions. While our institution is fortunate to have a multidisciplinary NES clinic that includes a psychiatrist and a social worker to assist with diagnosing and managing these comorbidities, it is unrealistic to expect most patients with NES to have access to such comprehensive care [26].

Despite being among the most consistently and strongly associated psychiatric comorbidities with NES, PTSD was the most frequently "missed" diagnosis among our referred patients [3,34,35]. When combining patients that received a diagnosis of PTSD or were documented by our behavioral health team to have significant trauma-related symptoms with those that screened positive by SPRINT, 86% of our patients show some evidence of significant trauma-related symptomatology. When compared to the referral data suggesting 43% of patients with a diagnosis of PTSD, this reflects an additional 43% that may stand to benefit from targeted treatment of their trauma-related symptoms. The reasons for these discrepancies are not clear, though there are several hypotheses. There may be increased stigma associated with PTSD and trauma compared to other psychiatric diagnoses and both patients may be reluctant to report this information, and providers may be hesitant to inquire due to perceptions of trauma being even more sensitive or time consuming to discuss with patients in otherwise busy clinical settings. Is there a perception on behalf of providers that anxiety and depression are easier to assess for and discuss with patients compared to trauma and PTSD? Further work is needed to better evaluate this apparent difficulty in eliciting PTSD and trauma-related symptoms within this population.

The rates of substance abuse in our studied population were low and there was little variability between referral and after intake diagnoses. This is in stark contrast to prior work that found 64% of male, veteran patients with nonepileptic seizures had histories of substance abuse [27]. Men have well-documented increased rates of substance abuse compared to women, and veterans have higher rates of alcohol abuse compared to non-veterans [28,29]. This may help explain our low rates given that our population is primarily non-veteran women. However, based on the proportion of our patients diagnosed with PTSD alone, prior studies suggest higher rates of substance abuse would be expected [30,31]. One potential explanation for this is that the nature of a 6- or 18-week, intensive group therapy treatment modality selects against patients with significant substance abuse problems that could limit follow-up or participation in group therapy. In addition, as with all the studied comorbidities, it remains possible that patients are not volunteering accurate information regarding their substance use. We suspect that the strong link between many substances and electrographic seizures, either through acute intoxication or withdrawal syndromes, prompts providers to carefully investigate these comorbidities when evaluating patients presenting with possible epileptic versus nonepileptic seizures, and ultimately resulted

Table 4
Summary of psychiatric comorbidities and chronic pain documented at referral compared to after clinic intake.

Diagnosis (n = 167)	At referral	After intake	Diagnosis Added	Diagnosis Removed	Cohen's Kappa	Percent Agreement
PTSD	71 (43%)	103 (62%)	35 (21%)	3 (2%)	0.56 (0.45–0.68)	77%
Depression	103 (62%)	101 (60%)	11 (7%)	13 (8%)	0.70 (0.59–0.81)	86%
Anxiety/Panic	90 (54%)	99 (59%)	18 (11%)	9 (5%)	0.67 (0.56 to 0.78)	84%
Bipolar Disorder	31 (19%)	25 (15%)	3 (2%)	9 (5%)	0.74 (0.61 to 0.88)	93%
Schizophrenia	4 (2%)	2 (1%)	0 (0%)	2 (1%)	0.66 (0.22–1)	99%
Chronic pain or Fibromyalgia	34 (20%)	33 (20%)	5 (3%)	6 (4%)	0.80 (0.68 to 0.91)	93%

95% CI of Cohen's Kappa values are shown in parentheses.

Table 5
Summary of substance abuse documentation at referral compared to after clinic intake.

Diagnosis (n = 167)	At referral	After intake	Diagnosis Added	Diagnosis Removed	Cohen's Kappa	Percent Agreement
Substance Abuse	3 (2%)	2 (1%)	0 (0%)	1 (0.5%)	0.8 (0.41–1)	99%
Alcohol Abuse	5 (3%)	5 (3%)	0 (0%)	0 (0%)	1 (1–1)	100%
Marijuana Use	4 (2%)	5 (3%)	1 (0.5%)	0 (0%)	0.89 (0.66–1)	99%
Nicotine Use	8 (5%)	10 (6%)	3 (2%)	1 (0.5%)	0.77 (0.54 to 0.99)	98%

95% CI of Cohen's Kappa values are shown in parentheses.

Table 6
Summary of suicidality and self-injurious behavior documented at referral compared to after clinic intake.

Diagnosis (n = 167)	At referral	After intake	Diagnosis Added	Diagnosis Removed	Cohen's Kappa	Percent Agreement
Self-Injurious Behavior	10 (6%)	11 (7%)	1 (0.5%)	0 (0%)	0.95 (0.85–1)	99%
Suicidal Ideation	14 (8%)	14 (8%)	1 (0.5%)	1 (0.5%)	0.92 (0.82–1)	99%
Suicidal Attempt	14 (8%)	14 (8%)	1 (0.5%)	1 (0.5%)	0.92 (0.82–1)	99%

95% CI of Cohen's Kappa values are shown in parentheses.

Table 7
Comparison of PHQ9 scores between patients with no depression versus those with significant unipolar depressive symptoms.

PHQ9 Score	No depression N = 52	Unipolar Depression N = 101
4 or less	7 (13%)	12 (12%)
5–9	10 (19%)	14 (14%)
10–14	15 (29%)	22 (22%)
15–19	8 (15%)	17(17%)
20–27	6 (12%)	15 (15%)

Between patients with significant depression symptoms and those without, no significant difference was observed by Chi-Square test on PHQ9 scores.

Table 8
Comparison of GAD7 scores between patients with no anxiety or panic symptoms versus those with significant anxiety or panic symptoms.

GAD7 Score*	No anxiety or panic symptoms N = 68	Anxiety or panic symptoms N = 99
4 or less	20 (29%)	12 (12%)
5–9	18 (26%)	21 (21%)
10–14	10 (15%)	23 (23%)
15–21	13 (19%)	31 (31%)

*P value <0.05 by Chi-Square test comparing GAD7 scores between patients with anxiety or panic symptoms and those without symptoms.

in almost no discrepancy between at referral and after intake data regarding these diagnoses.

The estimated lifetime prevalence of suicide attempts is 2.7%, with a prevalence of suicidal ideation of 9.2% [32]. Among patients with epilepsy, a recent meta-analysis suggests prevalence of suicide attempts and ideation are 7.4% and 23.2%, respectively [33]. Our study found a similar rate of suicide attempts among nonepileptic seizure patients of 8%. Curiously, all the patients that reported a history of suicidal ideation had a history of a suicide attempt. This likely suggests an underdiagnosis of suicidal ideation as it seems extraordinarily unlikely that everyone with nonepileptic seizures in our population that contemplated suicide ultimately made an attempt. Additionally, while suicidal ideation requires patient report, prior suicide attempts are often well-documented in the chart if they resulted in medical care and may explain some of this discrepancy.

Mental health and substance abuse disorders are frequently underreported by patients and stigma surrounding psychiatric disease continues to be a barrier to patients seeking help [36,37]. Disparities in health outcomes, and even mortality, among patients

Table 9
Comparison of SPRINT score between patients with no PTSD or trauma-related symptoms versus those with PTSD or significant trauma-related symptoms.

SPRINT Score*	No PTSD N = 63	PTSD N = 103
Less than 14	22 (35%)	15 (15%)
14 or greater	41 (65%)	88 (85%)

*P value <0.01 by Fisher's exact test comparing SPRINT score with cutoff value of 14 between patients with PTSD or trauma-related symptoms and those without PTSD or other trauma-related symptoms.

with mental health disorders are well documented, with stigma among healthcare providers posited to play a role [38–40]. The stigma surrounding functional neurological disorders has also been well described and may be driven by arbitrary distinctions between "mental illness" and "brain diseases," that are referred to separate psychiatrists and neurologists, respectively, for primary management [41,42]. Critical to overcoming stigma is the ability to build rapport and trust between patient and provider, which can

take considerable time [43]. As the luxury of time is frequently in short supply in the emergency room or busy clinic when the patient with NES is first encountered, educational initiatives are needed to better equip providers to elicit these comorbidities within the constraints of our modern healthcare system [44].

There are several limitations to this study. The nature of a chart review study relies on patient recall and report of details of their medical history as well as the ability of providers to elicit and document this information. Most of the data in this study are sensitive, stigmatized information that patients may be reluctant to report, and about which providers may be reluctant to inquire. The nature in which psychiatric diagnoses are made and documented in the chart, particularly by non-psychiatrists, also provides a significant challenge. When reviewing primary care, emergency room, and other neurologist referrals we rarely encountered formal psychiatric diagnoses described by the DSM-V [9]. Instead of major depressive disorder or major depressive episode, statements like "the patient reports a history of depression" or "the patient endorses significant anxiety" are much more common. While we attempted to capture all patients with referral data suggestive of pathological symptoms, the non-standard nature in which psychiatric disease is documented by non-psychiatrists may have contributed to some mis-categorization of patients' "at referral" data. The population studied was primarily white women, and while rates of nonepileptic seizures are increased in women, this may limit generalization to other populations, including men and other ethnic or racial backgrounds. Given the rigors of attending an intensive 6- or 18-week program, there may be a selection bias toward patients that are able to meet this commitment. This may have skewed our population toward lower rates of substance abuse as discussed above, but also toward patients with reliable transportation or other socioeconomic factors that allow them to attend. Similarly, patients with less frequent or severe NES may not have been referred as often such that our population had higher rates of psychiatric comorbidity (if we assume more severe NES correlates with psychiatric disease).

5. Conclusion

This cross-sectional, chart review study confirms the well-documented association between psychiatric disease and NES and suggests that the actual burden of psychiatric disease and specifically PTSD, is even greater than neurologists, primary care providers, and emergency room providers might suspect based on the burden of psychiatric disease they report when referring patients for formal treatment of NES. After formal intake into our NES clinic where evaluation by a behavioral health provider occurs, 21% of these patients were documented to have a diagnosis of PTSD or clinically relevant trauma-related symptoms that were not mentioned at the time of the referral. Additionally, while 17% of patients referred to our clinic did not appear to have any psychiatric comorbidity, after intake this number was reduced to only 9% of patients, and among those 9%, screening scales administered at intake picked up significant symptoms of depression, anxiety, and PTSD, even if they did not meet criteria for diagnosis. These patients also have higher rates of suicidality than the general population, with 8% of our patients reporting a prior suicide attempt, suggesting the stakes are high regarding whether these diagnoses are made and appropriate treatment and safety measures, if needed, are pursued.

Despite the high prevalence of functional neurological disorders [45], comprehensive care in a center that specializes in treating patients with NES is not widely available for the overwhelming majority of patients. There are significant issues surrounding access to care of psychiatric illness in the United States and around the world, but this care remains much more widespread than the availability of clinics such as ours at the University of Colorado for nonepileptic seizures. Functional neurological disorders have the reputation for being difficult to treat and effectively "harmless" with regard to morbidity and mortality, but recent work suggests there is significant mortality associated with nonepileptic seizures [46]. While at present challenges exist to the widespread implementation and access of care dedicated to the treatment of NES, the underdiagnosis suggested by this study within a population that has long established high rates of psychiatric disease, should prompt providers to be more aggressive in their pursuit of identifying these comorbidities, and make the appropriate referrals for treatment as necessary.

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Drs. Lenio, Libbon, and Strom have clinical responsibilities that include the diagnosis and treatment of patients with nonepileptic seizures. Otherwise, none of the authors declare any conflicts of interest. We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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