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Psychiatric Comorbidities in Functional Neurological Disorders and Psychogenic Non-Epileptic Seizures: A Systematic Review and Policy Recommendations for Improving Assessment and Treatment

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Background: Psychogenic Non-Epileptic Seizures (PNES) and Functional Neurological Disorders (FND) are progressively attracting the attention of healthcare professionals both in the medical or surgical specialties and in psychiatric ones.

Methods: Due to FND and PNES complex presentation, often comorbid with other neurological, medical, and psychiatric conditions, starting from our experience with patients presenting with both conditions, we conducted a systematic review of articles that address the comorbidity of PNES and FND with other psychiatric conditions.

Results: Our review supports the point that PNES and FND are not autonomous conditions but develop on the grounds of other psychiatric comorbidities including autism, borderline personality disorder (BPD), post-traumatic stress disorder (PTSD), and alexithymia. Persons with PNES and FND have often a history of child abuse, neglect, and trauma, and these conditions can also trigger the two conditions if appearing later in life. We also propose policies to endorse the comorbidity theory and improve assessment and treatment.

Conclusion: The scrutinized studies confirm that PNES and FND might be comorbid or represent manifestations of what we hypothesize as an integrated biopsychosocial model where early trauma, abuse, and neglect lead to a progressive neuro sensitivity that can present in the same person, usually young female patients, as a combination of dysthymia, alexithymia, autism, PTSD, BPD, FND, and PNES.

Keywords: functional neurological disorder, psychogenic non-epileptic seizures, comorbidity, psychiatry, borderline personality disorder, autism, post traumatic stress disorder, alexithymia

Introduction

The World Health Organisation – International Classification of Diseases (WHO ICD-11) classifies Functional Neurological Disorder (FND) and Psychogenic Non-Epileptic Seizures (PNES) in 6B60 as *Dissociative Neurological Symptom Disorder* characterized by the manifestation of motor, sensory, or cognitive symptoms that suggest an involuntary disruption in the typical coordination of motor, sensory, or cognitive functions.[1] These symptoms do not align with any known nervous system disease, mental or behavioral disorder, or other medical condition.[1] The symptoms are not present just during another dissociative illness and are not caused by the effects of a drug or medicine on the central nervous system, including withdrawal effects or a Sleep-Wake disorder.[1] Subclassifications include (1) visual disturbance (6B60.0) such as blindness, tunnel vision, diplopia, visual distortion, or hallucinations; (2) auditory disturbance (6B60.1) with loss of hearing or auditory hallucinations; (3) vertigo (6B60.2) or dizziness; (4) other sensory

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disturbance (6B60.3) such as numbness, tightness, tingling, burning pain, or other symptoms related to touch, smell, taste, balance, proprioception, kinaesthesia, or thermoception; (5) speech disturbance with dysphonia, aphonia or dysarthria; (6) paresis or weakness; (7) gait disturbance with difficulty in walking, including ataxia; (8) movement disorder such as chorea, myoclonus, tremor, dystonia, facial spasm, parkinsonism or dyskinesia; and (9) cognitive symptoms with impaired memory language and other cognitive areas; (10) other symptoms.[1]

Psychogenic Non-epileptic Seizures (PNES) are episodes of altered movement, emotion, sensation, or experience similar to those due to epilepsy but which have purely emotional causes.[2] Some characteristics of PNES are the preserved memory for the events antecedent, during, and after the episodes with a duration of more than two minutes, with rapid recovery after the event, with no post-ictal confusion, and the patient asking what has happened.[3]

FND is a condition affecting many young people.[3] It is estimated an incidence of 4–12/1000,000 population per year, with the motor FND affecting 4–5/100,000 per year and PNES 1.5–4.9/100,000 per year.[3] The estimated prevalence for FND is 50/100,000 and for PNES 2–33/100,000 persons.[3] Patients with FND make up 9% of neurology admissions, 16% of neurology clinic referrals, and 10–25% of patients referred to epilepsy specialist centers.[4] In patients with PNES the annual cost of antiepileptic medication is about 160 dollars, and the cost for diagnostic tests up to a maximum of 1600 dollars.[5] A systematic review of 16 studies in the USA reported that the cost of FNS is direct costs that represent resources used for health care (eg, cost of investigations or the time spent on assessment by a doctor) in contrast, indirect costs represent productivity losses arising from morbidity-related sickness absence (eg, loss of employment, benefits, or the cost of childcare while hospitalized).[4] In the USA, the annual cost per person with FND is USD 46,000.[6] In a study in Ireland, it was calculated that the annual cost of PNES per patient is about Euro 21,000 Euro, while the combined cost of diagnosis and psychological treatment is about Euro 9000.[7]

The literature proposes that FND and PNES could be comorbid with other psychiatric conditions. Due to the complexity of these diagnoses and the length of time it takes to assess and confirm them, it is vital that practitioners are aware of other comorbidities that might be the underlying triggers or presentations of FND and PNES. Therefore, the current review aimed to extract evidence of comorbid psychiatric conditions in FND and PNES and make policy recommendations.

Methods

Review Questions

Q1: Are FND and PNES comorbid with any known psychiatric conditions?
Q2: What are the extractable policy recommendations if the theory of comorbidity is confirmed?

Review Objectives

O1: To extract from the current literature evidence of psychiatric comorbidities in FND and PNES.
O2: To find any other factor associated with PNES and FND.
O3: To craft policies and recommendations reflecting the comorbidity theory.

Data Extraction

Literature Search

The study occurred from January 2024 to August 2024. PRISMA flowchart helped us extract salient literature and to condense our search findings (Figure 1).[8] All articles selected were open access or we had access to them through the academic library database. All articles were in English and peer–reviewed. Exclusion criteria were articles not in English and studies where FND and PNES were not diagnosed although present. The databases used were PubMed, Scopus, Web of Science, Google Scholar, Google, PsychINFO, and Medline. The keywords were "psychogenic non$pileptic seizure*", "functional neurological disorder*", "comorbidit*","borderline personality disorder', "emotionally unstable personality disorder", "autism", "PTSD", "Post Traumatic Stress Disorder", "FND", and 'PNES'. The Boolean connectives were "AND, OR". When conflicts in the search existed between authors, the most senior helped choose relevant articles. We used Cochrane GRADE-Pro GDT framework

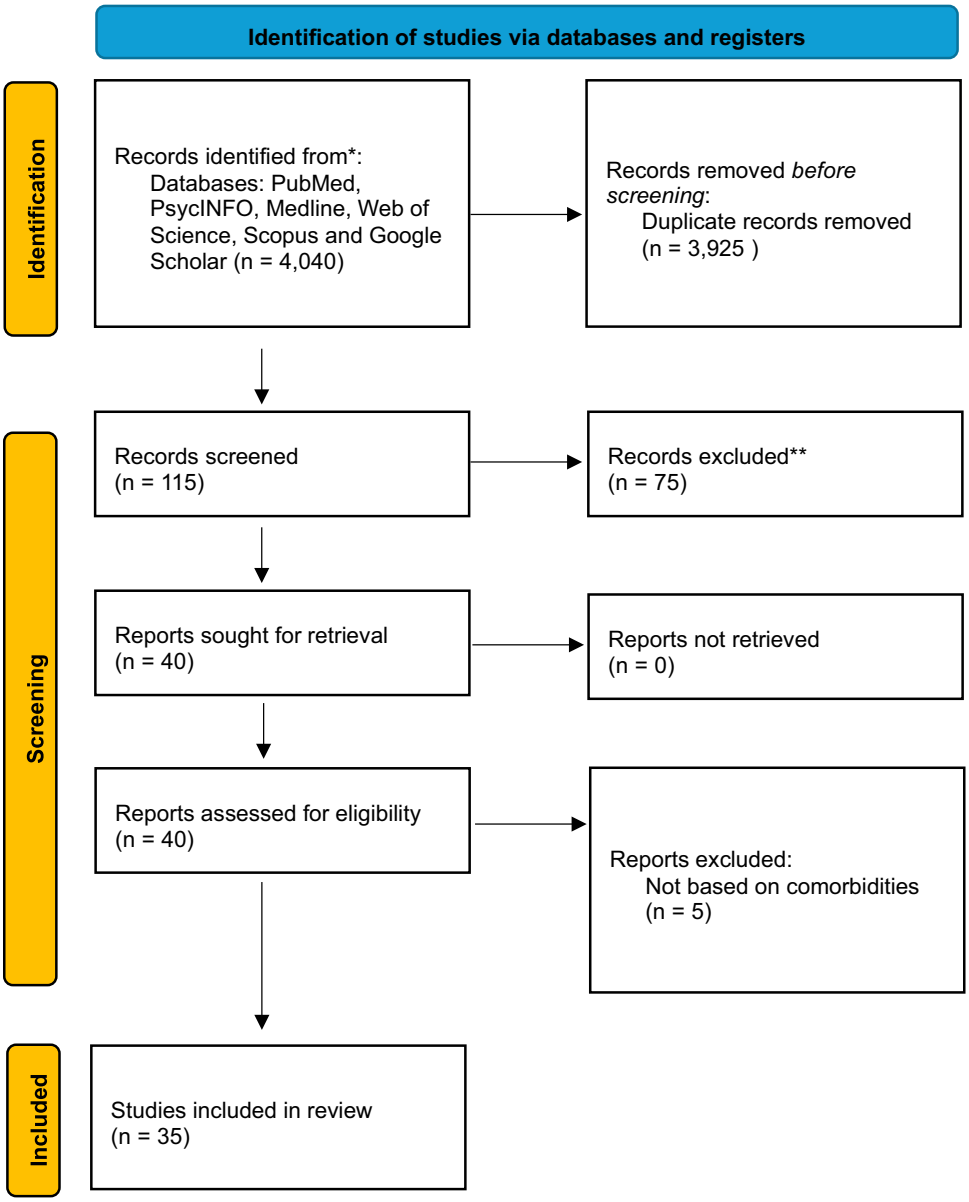

Figure 1 PRISMA Flowchart. Adapted from Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021; 372. Creative Commons.[8]

(https://www.gradepro.org/) to summarize our findings and create the template for policy recommendations (Tables 1 and 2).[9–11] GRADE assessment allows the analysis of risk of biases or search results, extracts the outcomes and defines the grade of certainty in the results. The domains extractable by GRADE are (1) *risk of bias* both at the study level and outcome, (1) *inconsistency* here focused on clinical heterogeneity, (3) *indirectness* with the best evidence extractable by direct comparisons between treatments and conducted with a population and setting similar where the recommendation will be implemented, (4) *imprecision*, linked to the precision of the estimate of the population applicable from the sample, and (5) *publication bias* related to the likelihood that results have influenced the publishing outcomes.[9–12] Large effects ensue with robust research results, limited biases, and strong statistical relationships in the outcomes.[12] The PICO framework helped in the inclusion criteria (https://www.cochranelibrary.com/about-pico).

Table 1 Search Results from Database

Field	Search	Number of findings
PubMed		
(Psychogenic Non-Epileptic Seizure*) AND (Comorbidit*)	("psychogenic"[All Fields] OR "psychogenically"[All Fields] OR "psychogenicity"[All Fields] OR "psychogenous"[All Fields]) AND "Non-Epileptic"[All Fields] AND "seizure*"[All Fields] AND "comorbidit*"[All Fields]	110
(Functional Neurological Disorder*) AND (Comorbidit*)	("functional"[All Fields] OR "functional s"[All Fields] OR "functionalities"[All Fields] OR "functionality"[All Fields] OR "functionalization"[All Fields] OR "functionalizations"[All Fields] OR "functionalize"[All Fields] OR "functionalized"[All Fields] OR "functionalizes"[All Fields] OR "functionalizing"[All Fields] OR "functionally"[All Fields] OR "functionals"[All Fields] OR "functioned"[All Fields] OR "functioning"[All Fields] OR "functionings"[All Fields] OR "functions"[All Fields] OR "physiology"[MeSH Subheading] OR "physiology"[All Fields] OR "function"[All Fields] OR "physiology"[MeSH Terms]) AND ("neurologic"[All Fields] OR "neurological"[All Fields] OR "neurologically"[All Fields]) AND "disorder*"[All Fields] AND "comorbidit*"[All Fields]	2634
((Comorbidit*) AND (Functional Neurological Disorder*)) AND (Borderline Personality Disorder)	"comorbidit*"[All Fields] AND (("functional"[All Fields] OR "functional s"[All Fields] OR "functionalities"[All Fields] OR "functionality"[All Fields] OR "functionalization"[All Fields] OR "functionalizations"[All Fields] OR "functionalize"[All Fields] OR "functionalized"[All Fields] OR "functionalizes"[All Fields] OR "functionalizing"[All Fields] OR "functionally"[All Fields] OR "functionals"[All Fields] OR "functioned"[All Fields] OR "functioning"[All Fields] OR "functionings"[All Fields] OR "functions"[All Fields] OR "physiology"[MeSH Subheading] OR "physiology"[All Fields] OR "function"[All Fields] OR "physiology"[MeSH Terms]) AND ("neurologic"[All Fields] OR "neurological"[All Fields] OR "neurologically"[All Fields]) AND "disorder*"[All Fields]) AND ("borderline personality disorder"[MeSH Terms] OR ("borderline"[All Fields] AND "personality"[All Fields] AND "disorder"[All Fields]) OR "borderline personality disorder"[All Fields])	8
((Comorbidit*) AND (Functional Neurological Disorder*)) AND (Autism)	"comorbidit*"[All Fields] AND (("functional"[All Fields] OR "functional s"[All Fields] OR "functionalities"[All Fields] OR "functionality"[All Fields] OR "functionalization"[All Fields] OR "functionalizations"[All Fields] OR "functionalize"[All Fields] OR "functionalized"[All Fields] OR "functionalizes"[All Fields] OR "functionalizing"[All Fields] OR "functionally"[All Fields] OR "functionals"[All Fields] OR "functioned"[All Fields] OR "functioning"[All Fields] OR "functionings"[All Fields] OR "functions"[All Fields] OR "physiology"[MeSH Subheading] OR "physiology"[All Fields] OR "function"[All Fields] OR "physiology"[MeSH Terms]) AND ("neurologic"[All Fields] OR "neurological"[All Fields] OR "neurologically"[All Fields]) AND "disorder*"[All Fields]) AND ("autism s"[All Fields] OR "autisms"[All Fields] OR "autistic disorder"[MeSH Terms] OR ("autistic"[All Fields] AND "disorder"[All Fields]) OR "autistic disorder"[All Fields] OR "autism"[All Fields])	164

((Comorbidit*) AND (Functional Neurological Disorder*)) AND (PTSD)	"comorbidit*"[All Fields] AND (("functional"[All Fields] OR "functional s"[All Fields] OR "functionalities"[All Fields] OR "functionality"[All Fields] OR "functionalization"[All Fields] OR "functionalizations"[All Fields] OR "functionalize"[All Fields] OR "functionalized"[All Fields] OR "functionalizes"[All Fields] OR "functionalizing"[All Fields] OR "functionally"[All Fields] OR "functionals"[All Fields] OR "functioned"[All Fields] OR "functioning"[All Fields] OR "functionings"[All Fields] OR "functions"[All Fields] OR "physiology"[MeSH Subheading] OR "physiology"[All Fields] OR "function"[All Fields] OR "physiology"[MeSH Terms]) AND ("neurologic"[All Fields] OR "neurological"[All Fields] OR "neurologically"[All Fields]) AND "disorder*"[All Fields]) AND ("stress disorders, post traumatic"[MeSH Terms] OR ("stress"[All Fields] AND "disorders"[All Fields] AND "post traumatic"[All Fields]) OR "post-traumatic stress disorders"[All Fields] OR "ptsd"[All Fields])	67
((Comorbidit*) AND (Psychogenic Non Epileptic Seizure*)) AND (Borderline Personality Disorder)	"comorbidit*"[All Fields] AND (("psychogenic"[All Fields] OR "psychogenically"[All Fields] OR "psychogenicity"[All Fields] OR "psychogenous"[All Fields]) AND "Non"[All Fields] AND ("epilepsy"[MeSH Terms] OR "epilepsy"[All Fields] OR "epileptic"[All Fields] OR "epileptics"[All Fields] OR "epileptic s"[All Fields] OR "epileptical"[All Fields] OR "epileptization"[All Fields]) AND "seizure*"[All Fields]) AND ("borderline personality disorder"[MeSH Terms] OR ("borderline"[All Fields] AND "personality"[All Fields] AND "disorder"[All Fields]) OR "borderline personality disorder"[All Fields])	3
((Comorbidit*) AND (Psychogenic Non Epileptic Seizure*)) AND (Autism)	"comorbidit*"[All Fields] AND (("psychogenic"[All Fields] OR "psychogenically"[All Fields] OR "psychogenicity"[All Fields] OR "psychogenous"[All Fields]) AND "Non"[All Fields] AND ("epilepsy"[MeSH Terms] OR "epilepsy"[All Fields] OR "epileptic"[All Fields] OR "epileptics"[All Fields] OR "epileptic s"[All Fields] OR "epileptical"[All Fields] OR "epileptization"[All Fields]) AND "seizure*"[All Fields]) AND ("autism s"[All Fields] OR "autisms"[All Fields] OR "autistic disorder"[MeSH Terms] OR ("autistic"[All Fields] AND "disorder"[All Fields]) OR "autistic disorder"[All Fields] OR "autism"[All Fields])	2
((Comorbidit*) AND (Psychogenic Non Epileptic Seizure*)) AND (PTSD)	"comorbidit*"[All Fields] AND (("psychogenic"[All Fields] OR "psychogenically"[All Fields] OR "psychogenicity"[All Fields] OR "psychogenous"[All Fields]) AND "Non"[All Fields] AND ("epilepsy"[MeSH Terms] OR "epilepsy"[All Fields] OR "epileptic"[All Fields] OR "epileptics"[All Fields] OR "epileptic s"[All Fields] OR "epileptical"[All Fields] OR "epileptization"[All Fields]) AND "seizure*"[All Fields]) AND ("stress disorders, post traumatic"[MeSH Terms] OR ("stress"[All Fields] AND "disorders"[All Fields] AND "post traumatic"[All Fields]) OR "post-traumatic stress disorders"[All Fields] OR "ptsd"[All Fields])	21

(*Continued*)

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Table 1 (Continued).

Field	Search	Number of findings
((Comorbidit*) AND (Functional Neurological Disorder*)) AND (Psychogenic Non Epileptic Seizure*)	"comorbidit*"[All Fields] AND (("functional"[All Fields] OR "functional s"[All Fields] OR "functionalities"[All Fields] OR "functionality"[All Fields] OR "functionalization"[All Fields] OR "functionalizations"[All Fields] OR "functionalize"[All Fields] OR "functionalized"[All Fields] OR "functionalizes"[All Fields] OR "functionalizing"[All Fields] OR "functionally"[All Fields] OR "functionals"[All Fields] OR "functioned"[All Fields] OR "functioning"[All Fields] OR "functionings"[All Fields] OR "functions"[All Fields] OR "physiology"[MeSH Subheading] OR "physiology"[All Fields] OR "function"[All Fields] OR "physiology"[MeSH Terms]) AND ("neurologic"[All Fields] OR "neurological"[All Fields] OR "neurologically"[All Fields]) AND "disorder*"[All Fields]) AND (("psychogenic"[All Fields] OR "psychogenically"[All Fields] OR "psychogenicity"[All Fields] OR "psychogenous"[All Fields]) AND "Non"[All Fields] AND ("epilepsy"[MeSH Terms] OR "epilepsy"[All Fields] OR "epileptic"[All Fields] OR "epileptics"[All Fields] OR "epileptic s"[All Fields] OR "epileptical"[All Fields] OR "epileptization"[All Fields]) AND "seizure*"[All Fields])	27
Medline and Web of Science		
Functional Neurological Disorder* AND Comorbidit* *		772
Functional Neurological Disorder* AND Comorbidit* AND Borderline Personality Disorder		10
Functional Neurological disorder* AND Comorbidit* AND Autism		29
Functional Neurological Disorder* AND Comorbidit* AND PTSD		10
Psychogenic Non Epileptic Seizure* AND Comorbidit* AND Borderline Personality Disorder		8
Psychogenic Non Epileptic Seizure* AND Comorbidit* AND Autism		4
Psychogenic Non Epileptic Seizure* AND Comorbidit* AND PTSD		22
Psychogenic Non Epileptic Seizure* AND Comorbidit* AND Functional Neurological Disorder*		18

Notes: Data from https://pubmed.ncbi.nih.gov; https://webofscience.com/wos.

Table 2 GRADE-Pro GDT Summary of Findings

Outcomes	Evidence	Authors	Non-randomized study type and assessment	Certainty of evidence (GRADE)
FND prevalence and causes	The study found that functional neurological disease (FND) commonly develops in children and adolescents. About 70% of FND cases are female, and the usual onset age is 13. Stressful life events, interpersonal issues, and adverse childhood experiences are harmful. FND patients are more likely than controls to experience stressful life events and maltreatment, such as emotional neglect and sexual and physical abuse, according to 34 retrospective investigations.	Mavroudis et al, 2024[13]	Systematic review	⊕⊕⊕⊕High
Epidemiology of FND	Twelve persons per 100,000 in the UK have FND, with 8000 new diagnoses annually. About 8000 new FND cases are diagnosed in the UK annually, impacting 50,000–100,000. Women are 3:1 more likely to experience FND. Men with symptoms increase with age.	Varley et al, 2024;[14] Bennett et al 2021[15]	Review	⊕⊕⊕⊕High
Clinical Psychopathology in FND	FND patients suffer more physical and psychological symptoms than individuals with comparable diseases. Additionally, they are more likely to have experienced unfavourable experiences in their childhood and lately.	Bennett et al, 2021[15]	Systematic review	⊕⊕⊕⊕High
	The authors discovered more depression, anxiety, alexithymia and severe dissociative symptoms among FND patients.	Cuoco et al, 2021[16]	Case-control study	⊕⊕⊕⊕High
	Interpersonal issues may imply undiagnosed maladaptive personality traits or a personality disorder like borderline or avoidant. They were mostly observed among women and those from low socioeconomic standing.	Lidstone et al, 2020[17]	Systematic review	⊕⊕◯◯Low
Comorbidities in FND	In a sample of 527 participants, the authors found that many had psychiatric comorbidities, including ADHD, OCD, PTSD, Depression, Bipolar Affective Disorder, Dissociative Disorder, and Fibromyalgia. In addition, there was a comorbidity with a high body mass index (BMI).	Ducroizet et al, 2023[18]	Survey	⊕⊕⊕◯Moderate
	In a sample of N=417, psychiatric comorbidities were suicidal ideation ($p<0.001$) and self-harm ($p=0.02$).	Macchi et al, 2021[19]	Retrospective cohort study	⊕⊕⊕◯Moderate
Comorbidity FND and childhood trauma	People who have endured stress and abuse are more likely to develop FND than healthy or patient controls. Due to its incidence of 49%, emotional neglect was more harmful than sexual abuse (24%) and physical abuse (30%). However, many cases do not record any prior stressful events.	Ludwig et al, 2018[20]	Case-control study	⊕⊕⊕◯Moderate

(*Continued*)

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Table 2 (Continued).

Outcomes	Evidence	Authors	Non-randomized study type and assessment	Certainty of evidence (GRADE)
Comorbidity FND and PTSD	Sample of 430 patients (69.3% females); 60.7% presented with PTSD with a similar rate between FND and PNES.	Gray et al, 2020[21]	Structured interviews; cross-sectional study	⊕⊕⊕◯Moderate
Comorbidity FND and urinary retention in women	Ninety–one women, averaging 34±11 years, were diagnosed with Fowler's syndrome. Psychiatric and psychological comorbidities were reported by 97% of subjects. In particular, 77% felt depression, 78% anxiety, and 32% PTSD. Self-harm was 14%, and personality problems 16%. The sample included 35% of women with childhood trauma.	Selai et al, 2024[22]	Structured clinical interviews	⊕⊕⊕◯Moderate
Psychiatric comorbidities in PNES	In this study, 53%–100% of PNES patients had mental comorbidities. Depression varied from 8.9% to 85%, anxiety from 4.5% to 70%, PTSD from 7% to 100%, personality disorders from 5.4% to 74.3%, and alcohol and drug addiction from 9.8% to 29.5%.	Diprose et al, 2016[23]	Systematic review and meta-analysis	⊕⊕⊕◯Moderate
	Mood and anxiety problems were 72.7% and 54.5% frequent in PNES patients. Cluster B personality disorder was more common in PNES patients (69.7%) than epilepsy patients (33.3%). The SCID II screen indicated a substantial increase in borderline and depressed personality disorders among PNES respondents ($p < 0.001$). The incidence of polydrug therapy was significantly greater in psychogenic seizure patients (75.8%) compared to epileptic seizure patients (45.5%) ($p < 0.05$).	Rady et al, 2021[24]	Case-control study	⊕⊕⊕◯Moderate
	In a cohort of 271 patients with PNES, PNES+possible/probably epilepsy and PNES+definite epilepsy depression was found to be present in 72% of cases, anxiety in 53.1%, history of emotional, physical or sexual abuse in 2.9%, other psychiatric disorders in 32.2%, personality disorder in 16.3%, substance abuse in 7.4%, and active suicidal ideation in 7.7%.	Massot-Tarrús et al, 2022[25]	Large–cohort study	⊕⊕⊕⊕High
Comorbidity PNES and PTSD	In this with study of 130 patients, PNES was postulated as indicative of PTSD.	Szaflarski et al, 2015[26]	Structured interviews and tests	⊕⊕◯◯Low
FND, PNES in Children and Family History	A family history of mental illnesses was found in 37% of patients (25% PNES, 12% FND). At 23% and 16%, anxiety and mood disorders were the most common. Patients had a family history of medical disease in 76% (46% PNES; 30% FND). Stressful or traumatic life experiences were reported by 67% of patients (37% PNES; 30% FNDs), including loss/death (30%), family troubles (28%), and bullying (28%).	Gigliotti et al 2023[27]	Case-control study	⊕⊕⊕⊕High

Comorbidity of BPD in PNES	Twenty patients with PNES: 10 had conversion disorder, six had borderline personality disorder, and four had a learning disability.	Lacey et al 2007;[28] Drake et al, 1992[29]	Clinical assessment	⊕⊕◯◯Low
	A review of 18 studies found a10% to 86% comorbidity.	Lacey et al, 2007[28]	Systematic review	⊕⊕⊕◯Moderate
	The group included 249 refractory seizure patients having video-EEG monitoring. In this sample, 30.4% of brain MRIs were abnormal. Personality disorders were found in 44.6% of PNES patients, with emotionally unstable (borderline) personality disorders being the most frequent at 32.1%.	Hovorka et al, 2007[30]	Clinical assessment: video EEG monitoring	⊕⊕⊕◯Moderate
Clinical characteristics of patients with refractory PNES	In PNES history, loved ones' deaths, recent deaths, sickness, injury, violence, and custody challenges were triggering events. Another factor was childhood trauma, including sexual abuse and parental separation. Clinical history included intellectual disabilities and bullying.	Fullam & Costello, 2024[31]	Clinical interview and 6-year follow-up	⊕⊕◯◯Low
	PNES is a response to severe chronic trauma, such as childhood or adult sexual assault, adult rape, marital rape, or psychical abuse. Internal family sexual abuse, physical abuse, aggression, emotional abuse, and neglect also affected early childhood attachment.	Quinn et al, 2008[32]	Review	⊕⊕◯◯Low
	The sample included 77 patients aged 36–55 (57.5% female). PNES was verified by video-EEG. PNES patients had higher anxiety scores and more maladaptive personality traits, including disinhibition and psychoticism, than epilepsy patients.	Kustov et al, 2024[33]	Case-control of PNES with Epilepsy alone	⊕⊕⊕◯Moderate
Comorbidity FND, PNES, and BPD	FND, BPD, and PNES are linked as from phenomenological studies of mental institutions and communities. PNES may become an "epidemic" in children and adolescent psychiatric inpatient units when the most prominent patient has it. All other (mainly female) patients replicate her behaviour, and the whole ward might experience PNES.	Lazzari & Rabottini, 2023[34]	Naturalistic ethnographic observations in inpatients and community psychiatry; follow-up 3 years	⊕⊕⊕◯Moderate
Comorbidity FND, Factitious Disorder and BPD	Naturalistic constant observations in inpatient settings. Comorbidity of FND and BPD, especially in female patients. Acute presentations of FND (eg, paraplegia) after admissions from Emergency Rooms in patients otherwise healthy. It is more common in young female patients with a diagnosis of BPD. It tends to have a chronic-remittent presentation and comorbidity with dysthymia and autism.	Lazzari et al, 2023[35]	Naturalistic ethnographic observations and case reports	⊕⊕⊕◯Moderate
Comorbidity FND and other psychiatric conditions	Patients are likely to suffer from dysthymia, anhedonia, panic attacks, past traumatic experiences (eg childhood maltreatment and adverse events in adulthood), and PTSD	Saxena et al, 2020[36]	Case studies	⊕⊕◯◯Low
Comorbidity FND and BPD	A 68-year-old FND/BPD lady. She presented with dissociation, which included depersonalisation and derealisation. FND was found linked to neurological system disruptions caused by trauma and interpersonal problems.	Tinlin-Dixon, 2024[37]	Case report	⊕⊕◯◯Low

(*Continued*)

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Table 2 (Continued).

Outcomes	Evidence	Authors	Non-randomized study type and assessment	Certainty of evidence (GRADE)
Comorbidity FND, PNES, and BPD	The authors describe a young woman presenting with FND and PNES with immobility on a wheelchair reliance.	Henry et al, 2021[38]	Case report	⊕⊕◯◯Low
	FND often causes paraplegia, wheelchair reliance, and double incontinence, which were not apparent at acute medical unit admission. It usually affects women with autism and BPD. Mutism is a new observed presentation.	Lazzari et al, 2016[39]	Naturalistic ethnographic observations and case studies	⊕⊕⊕◯Moderate
Comorbidity FND and Alexithymia	FND is associated with alexithymia, somatic symptoms, and depression.	de Vroege et al, 2023[40]	Structured interviews	⊕⊕◯◯Low
Comorbidity FND, Alexithymia, and Autism (ASD)	Comorbidity of FND with autism and alexithymia in adults.	Cole et al, 2023[41]	Structured interviews	⊕⊕⊕◯Moderate
Comorbidity FND and Autism	Of a sample of 344 responders diagnosed with FND, the mean age was 39.8 ± 11.6 years (female sex 90%). Eight percent reported a prior ASD diagnosis, and 24% reported a first-degree family with an official diagnosis of ASD, usually their children. For 69% of responders, there was a clinically significant ASD and 21% indicated autistic features.	González-Herrero et al, 2022[42]	Structured interviews	⊕⊕⊕◯Moderate
	Individuals who have ASD but do not have intellectual disability are at a higher risk of experiencing FND compared to the general population.	Nistico' et al, 2022[43]	Structured interview	⊕⊕⊕◯Moderate
Comorbidity between PNES, Epilepsy, and PTSD	A cohort study was divided into three groups: PNES-only, PNES+epilepsy, and PNES +Probably epilepsy. There were no significant variations in the prevalence of depression, anxiety, post-traumatic stress disorder (PTSD), drug misuse, or suicide ideation between the three groups, length and frequency of PNES episodes.	Alkhaldi et al, 2024[44]	Cohort study	⊕⊕◯◯Low
Psychiatric comorbidities in PNES	Among the 24 patients diagnosed with PNES, the most common comorbidities were PTSD (29%), affective disorders (54%), somatoform disorders (37.5%), and anxiety disorders (25%).	D'Alessio, 2006[45]	Standardized psychiatric interviews	⊕⊕⊕◯Moderate
Psychological aspects in PNES	The diagnosis was verified by inpatient vEEG. Clinical, true psychogenic nonepileptic seizures are not deliberate but rather a psychological defense mechanism to hide internal stressors. Trauma-related illnesses include PTSD, anxiety, depression, conversion, somatization, and dissociation. A borderline personality disorder is frequent.	Alsaadi & Marquez, 2005[46]	Clinical assessment	⊕⊕⊕◯Moderate

Differences between males and females with PNES	Compared to males with PNES, females with PNES presented with higher rates of depression, borderline personality disorder, suicidality, and childhood sexual abuse. Compared to females with PNES, males with PNES had a higher rate of substance use disorders.	Sullivan-Baca et al, 2023[47]	Retrospective chart review and comparison with groups with epilepsy	⊕⊕⊕◯Moderate
Personality cluster in PNES	The predominant cluster (50%) exhibited a resemblance to the profile often seen in individuals with borderline personality disorder. The second biggest cluster (44%) was marked by an excessively regulated personality. The third cluster (5%) showed similarities to the profile associated with avoidant personality disorder.	Reuber et al, 2004[48]	Dimensional clinical assessment of personality pathology - basic questionnaire (DAPP-BQ)	⊕⊕⊕◯Moderate
Comorbidity PNES and Autism in children and young people	About 16% of 59 children and young people with PNES had a diagnosis of ASD.	McWilliams 2019[49]	Structured interview	⊕⊕⊕◯Moderate
	PNEs can occur in children with undiagnosed autism	Miyawaki et al, 2016[50]	Case reports	⊕⊕◯◯Low
	Out of the 59 children and young people with PNES, 16.9% also had ASD. Individuals with ASD had a considerably higher likelihood of experiencing tics or ADHD compared to those without ASD.	McWilliams et al, 2019[49]	Retrospective analysis of data records	⊕⊕⊕◯Moderate
	In a population of 191 pediatric referrals for PNES, 4.7% had a diagnosis of autism spectrum disorder, and 3.1% had a diagnosis of intellectual disability. Most reported stressors included family difficulties, school worries, bullying, and peer hitches.	Freedman et al, 2023[51]	Cohort study	⊕⊕⊕◯Moderate
Comorbidity PNES and PTSD	PNES samples had rates of 44–100% trauma and 23–77% abuse, 15–40% greater than control groups. This shows that trauma may increase PNES risk. PNES samples had a greater frequency of PTSD than control groups, suggesting that PNES may be a clinical presentation of a dissociative PTSD subtype.	Fiszman et al, 2004[52]	Systematic review	⊕⊕⊕◯Moderate

Notes: Patient or population: Diagnosis of Functional Neurological Disorders and Psychogenic Non-Epileptic Seizures. Setting: Inpatient and outpatient psychiatric services, neurology departments for epilepsy, and other clinical departments. Intervention: Clinical assessments, EEG, formal and informal psychiatric interviews, retrospective studies, and systematic reviews. Comparison: Epileptic Seizures (ES) and Other Neurological Disorders, Autism, PTSD, BPD (Borderline Personality Disorder), Alexithymia, other psychopathologies. Table adapted from these studies.[9–11]

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Population

Persons of any age and gender attending general hospitals, neurology departments, clinics for epilepsy, and inpatient or outpatient psychiatric units with a diagnosis of FND and PNES.

Intervention

Standard clinical, neurological, and psychiatric assessments; use of targeted questionnaires; retrospective analysis of clinical records; ethnographic observations of units with persons with FND and PNES; EEG; patient's history of presenting conditions.

Comparisons

Comparison of persons with FND and PNES with others with epilepsy or other neurological conditions. Comparisons of patients before and after the presentation of FND and PNES. Comparison with Epileptic Seizures (ES) and Other Neurological Disorders, Autism, PTSD, BPD Alexithymia, and other psychopathologies. Costs for FND and PNES diagnosis and treatment compared with other conditions.

Outcomes

Development of FND and PNES. Outcomes after targeted psychopharmacological and psychotherapeutic interventions. Response to treatment and carers' support. Progression of symptoms after first assessment or intervention. Clinical outcomes after identification of FND and PNES.

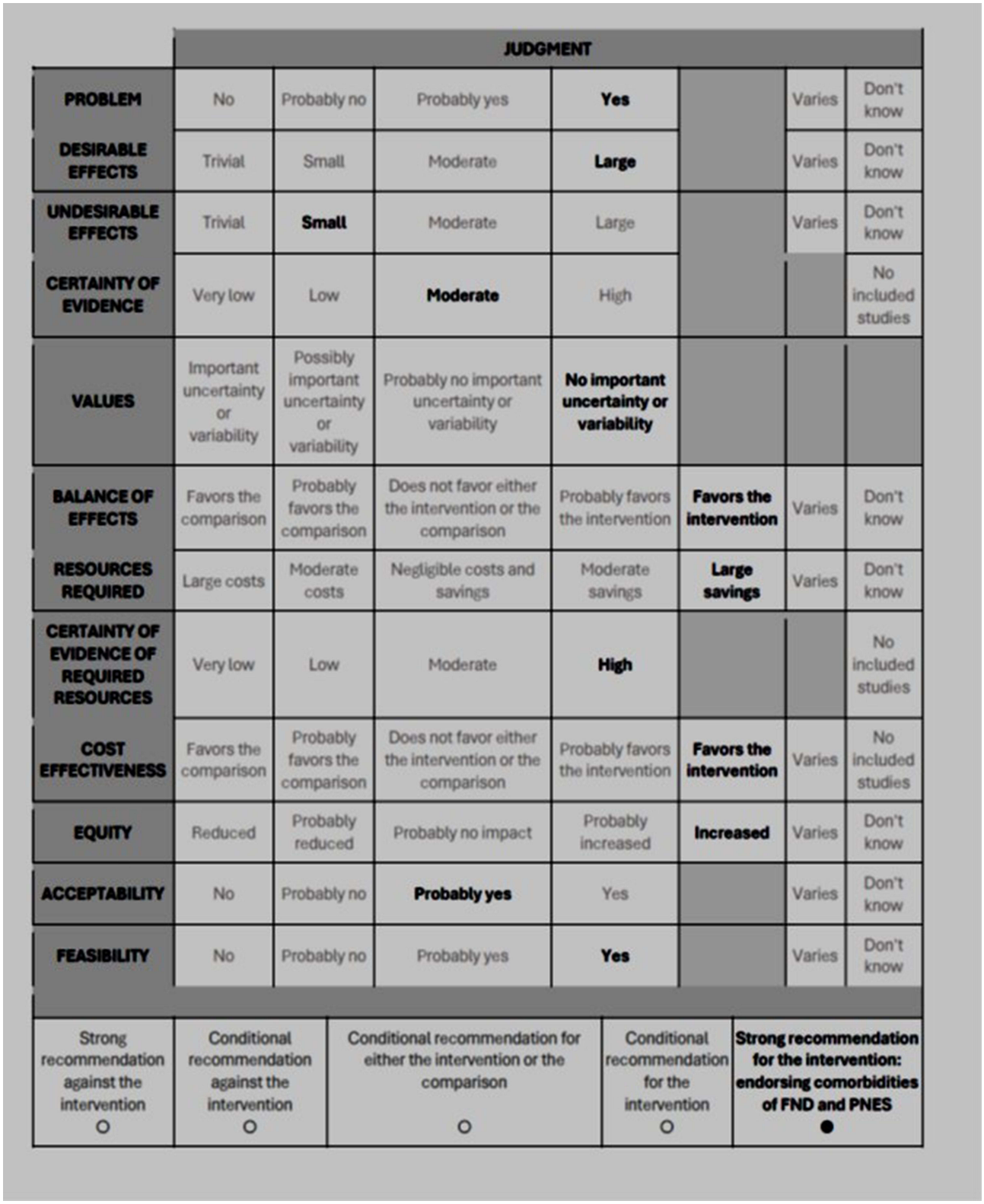
Qualitative Critical Analysis

As emerging from the literature, extracting comorbidities in FND and PNES helps direct diagnoses and policies while reducing the risks of long-term needless assessments and therapies. The review found that PNES and FND might be comorbid with PTSD, autism, BPD, alexithymia, and mild learning disability.[13–24,26–52] In specific, a history of childhood traumas or repeated sexual assaults, physical or emotional abuses, exposure to violence, and emotional neglect in children or adults might trigger PTSD, FND, and PNES.[13–24,26–52]

The majority of patients with FND and PNES are young women.[13–24,26–52] Persons with FND and PNES tend to have more frequent depression, dissociative disorders, alexithymia, PTSD, and anxiety compared to controls.[13–24,26–52] In our experience in children, adolescents and adult psychiatric wards, PNES and FND can be copied and assume "epidemic" dissemination from more influential patients to others in the group.[34,35,39]

Our ethnographic longitudinal study of PNES and FND in general adult psychiatric wards in the UK found that mostly affected were female patients, confirming what other authors found, and our diagnoses were BPD also comorbid to autism.[34,35,39] An empathic approach and placebo effect of provided medication were seen to resolve PNES crises.[34,35] For example, we found rapid resolution of crises, with low doses of anti–anxiety medications or anti–histamines, when we explained to these patients that these medications could help them or address their symptoms. In our population, FND usually presented with the sudden appearance of paralysis and wheelchair dependence in persons who were otherwise fit at the moment of self-referral at emergency departments.[34,35,39] The paralysis FND evolved in making these female patients bed-ridden in medical departments while and shortly after they developed double incontinence; no medical or neurological causes were found in all cases.[34,35,39]

In our qualitative ethnographic research in general adult psychiatric wards and liaison psychiatry attached to emergency departments in the UK, and in men, FND was mostly comorbid with factitious disorder, and the neurological "shakes, foggy mind and memory problems" were allegedly related to a secondary gain in aiming for hospital admission.[53] The degree of evidence of our review findings was low to moderate due to the absence of randomized studies. Another limitation was the presence of different diagnostic criteria adopted in each study, which has made the comparison complex. In the assessment, several instruments were adopted, from visual EEG (vEEG) to structured interviews, psychiatric scales, retrospective analyses, and case reports. We also found that some studies reported only general symptoms such as "depression", and "anxiety" while others tried to contextualize psychiatric symptoms into official psychopathological diagnoses.



	JUDGMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	**Large savings**	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	**Increased**	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ○	**Strong recommendation for the intervention: endorsing comorbidities of FND and PNES** ●

Figure 2 GRADEPro policy table. FND and PNES are considered clinical problems across several healthcare specialties. There are desirable effects in endorsing a comorbidity theory. We could not predict undesirable effects in confirming the comorbidity of FND and PNES with other psychiatric and neurodevelopmental conditions. From the literature collected and the lack of robust experimental data, the overall evidence for the comorbidity theory was usually moderate. We could not detect significant uncertainties or variabilities in the scrutinized evidence. The overall review would favor the intervention or conclusion about the comorbidity hypothesis, allowing substantial savings in assessing and treating FND and PNES. Cost-effectiveness is advantageous in the comorbidity model. Health equities will be improved, and persons with FND and PNES will receive adequate assessment and treatment. By endorsing the comorbidity model, patients with these conditions and their families will welcome this aspect, although some might still feel "misunderstood". Using a comorbidity model is workable and is currently applied in several medical and psychiatric settings in the UK. (Adapted from GRADEpro GDT. GRADEpro Guideline Development Tool [Software]. McMaster University and Evidence Prime, 2024. Available from: https://www.gradepro.org).[10]

Policy Recommendations

In this case, we used the GRADE-Pro GDT framework to complete the analysis of the comorbidity theory and make our policy recommendations (Figure 2)[9,11]:

1. *Is the problem a priority?*[9,11] From the review, we hypothesize that there is moderate to high evidence that FND and PNES might be comorbid with autism, borderline personality disorder, alexithymia, PTSD, and mild learning disability. These could be a unique picture likely to occur in persons with a history of childhood and adulthood trauma.
2. *How substantial are the desirable anticipated effects?*[9,11] We hypothesize large desirable effects in endorsing the comorbidity theory. The selected research suggests a long-term presentation for a condition refractory to immediate pharmacological support. We scrutinized and shared the impression that the difficulty of diagnosis and patients' resistance to accepting a "psychological explanation" of their condition can affect the recovery process.
3. *How substantial are the undesirable anticipated effects?*[9,11] We predict that these are small as there are no anticipated undesirable effects in endorsing the diagnosis of comorbidities of FND and PNES with autism, PTSD, alexithymia, and BPD.
4. *What is the overall certainty of the evidence of effects?*[9,11] When any research was conducted with a large sample, the effect of the evidence was moderate to large in favor of the comorbidity of FND and PNES. There was also a consensus on the existence of a history of former psychosocial traumas, childhood abuse, and earlier stressful events as triggers of FND and PNES.
5. *Is there important uncertainty about or variability in how much people value the main outcomes?*[9,11] We could not detect significant uncertainties in the outcomes of the selected research.
6. *Does the balance between desirable and undesirable effects favor the comorbidity theory?*[9,11] The extracted evidence from the literature favors the comparison and the assumption that FND and PNES have comorbid psychiatric conditions. There are no predicted undesirable effects in endorsing the theory that FND and PNES have comorbid BPD, autism, alexithymia, and PTSD. Favoring this assumption will improve the efficacy of psychological and psychiatric interventions.
7. *Resources required.*[9,11] We predicted a large saving as there is an expected gain in assessment and intervention if clinicians can consider psychiatric comorbidities in FND and PNES with a reduction of further diagnostic procedures and anti-seizure medication (unless used as mood stabilizers, as in BPD and PTSD). Endorsing these comorbidities will facilitate targeted and quick interventions supporting a combined psychological, psychotherapeutic, and neurological intervention.
8. *What is the certainty of the evidence of resource requirements (cost)?*[9,11] There is high evidence that undiagnosed psychiatric comorbidities in FND and PNES result in prolonged and expensive assessments and interventions. However, early diagnosis could reduce the costs of further unnecessary diagnostic procedures and medication while redirecting efforts and assets to explore the impact of the underlying comorbidities and causes.
9. *Does the cost-effectiveness of the comorbidity theory favor it?*[9,11] The confirmation of psychiatric comorbidities in PNES and FND favors multidisciplinary interventions, including psychiatric assessments and interventions.
10. *What would be the impact on health equity?*[9,11] Pursuing the comorbidity route and allowing a deeper understanding of the biopsychosocial model underlying the comorbidity theory will increase health equity. Furthermore, the history of childhood traumas, neglect, and violence should promote better policies for the protection of vulnerable children and persons.
11. *Is the theory of comorbidity acceptable to key stakeholders?*[9,11] There is the likelihood that once a diagnosis of psychiatric comorbidity of FND and PNES is posed, significant stakeholders will be able to understand the underlying mechanisms of their distress and undergo a targeted psychotherapeutic and psychological intervention to address the root causes of it (eg, PTSD and childhood trauma).

12. *Is the comparison theory feasible to implement?*[9,11] The intervention of supporting psychiatric comorbidity is possible to implement. However, constraints might be linked to the long and complex support needed for persons with FND and PNES. Nonetheless, a multidisciplinary team intervention (neurological, medical, and psychiatric) can be more successful once the comorbidity diagnosis is posed.

Discussion

The evidence supports the recommendations for endorsing the comorbidity theory for FND and PNES. The current review has highlighted the complexity of FND and PNES in the diagnosis and treatment. FND and PNES often face significant challenges in both diagnosis and social perception, primarily due to their complex and multifaceted nature.[54] Misdiagnosis is a frequent issue; patients are sometimes incorrectly labelled with psychiatric disorders or other neurological conditions because FND symptoms can closely mimic those of more well-known diseases.[55] This diagnostic ambiguity can lead to inappropriate treatments, exacerbating the patients' conditions and prolonging their suffering.[56]

The stigma surrounding FND further complicates the lives of those affected. Many people, including healthcare providers, may mistakenly believe that symptoms are "all in the head", leading to dismissive attitudes and inadequate care.[56] This stigmatization not only affects individuals but also ripples through communities, fostering misunderstanding and isolation; as a result, patients may feel marginalized or reluctant to seek help, perpetuating a cycle of neglect and mistreatment.[57] Treatment for PNES and FND includes facilitating understanding and acceptance of the diagnosis, addressing predisposing, precipitating, and perpetuating factors within the biopsychosocial model while addressing psychiatric comorbidities.[58] Some advocated treatments include psychotherapy, physical therapy, occupational therapy, speech therapy, pharmacotherapy, hypnosis, and neuromodulation.[58]

Another approach to treat PNES suggests a tripartite phase with (1) an initial stage where patients are helped to understand their diagnosis as they might question its accuracy, (2) the second phase of treatment includes psychotherapy and psychopharmacology also addressing psychiatric comorbidities, and (3) final phase is a long-term functional recovery.[58] There are hidden impacts of PNES on the community. PNES are often shrouded in misunderstanding and stigma, leading to significant repercussions for both individuals and the broader community.[59] The misdiagnosis of PNES as epilepsy is alarmingly common, primarily due to overlapping symptoms and a lack of awareness among healthcare professionals.[60]

This misdiagnosis not only delays appropriate treatment but also exposes patients to unnecessary antiepileptic medications, which might have severe side effects[61] unless these last are used as mood stabilizers in BPD and PTSD.[34] However, the withdrawal of anti-seizure medication in patients with PNES is more likely to occur if the treatment is started during the Epilepsy Monitor Unit and in the absence of structural brain lesions.[67] The societal stigma surrounding PNES exacerbates the issue. Individuals with PNES frequently face skepticism regarding the legitimacy of their condition, as it is perceived to be "invented".[62] Moreover, the lack of understanding within the community fosters a culture of silence and shame, preventing those affected from seeking help or discussing their experiences openly.[63] Major interventions include cognitive behavioural therapy, neurobehavioral therapy, group therapy, mindfulness-based therapy, hypnosis, eye movement desensitization and processing (EMDR), and EEG biofeedback.[64]

In PNES patients, psychiatric comorbidities are common while only 5% of PNES patients have no mental condition or stressor; moreover, up to 80% of PNES patients have a history of trauma or abuse, and they may reveal this history during a rigorous and sympathetic stress assessment.[65] However, long-term outcome studies in PNES demonstrate that many patients remain symptomatic and have quality of life and functioning problems.[66]

We propose an *integrated theoretical psychopathological model* to explain FND and PNES as extractable from the survey and corroborated by our clinical experience with persons with FND and PNES. We are inclined to endorse that childhood trauma, violence, and neglect, which can also appear late in childhood or adulthood and mostly in sensitive

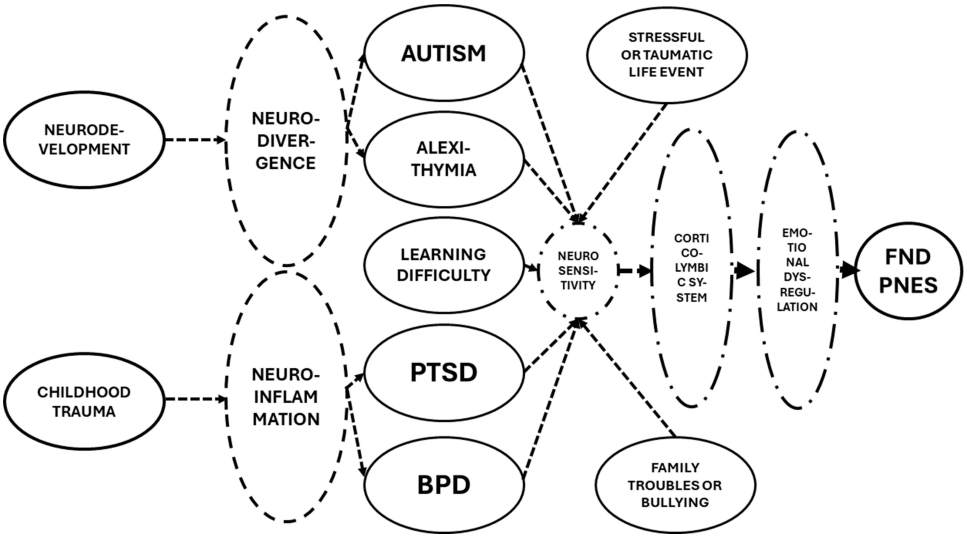


Figure 3 The biopsychosocial model of FND and PNES. Data from Lazzari et al.[67]

women, can represent the triggers for the development of the comorbidities in FND and PNES. This hypothesis also resonates with our biopsychosocial model postulating that neuroinflammation, consequent to childhood traumas, affects the corticolimbic system, which would make a person highly neuro-sensitive with direct loops going from emotions to the autonomic nervous system (Figure 3).[67]

Conclusions

The current review has highlighted the complex relationships between FND, PNES, and other neurological and psychiatric conditions. The literature extracted seems to support the idea that FND and PNES emerge from a complex array of psychiatric comorbidities, are often difficult to diagnose, and require extensive assessment and interventions until a final diagnosis is posed. Also emerging from the scrutinized literature is the need for integrated and multi-disciplinary investigations and treatments. The clinicians that usually come across FND and PNES are neurologists, psychiatrists and general medicine practitioners. They should make a full assessment to rule out any underlying organic cause. Once this process has terminated the psychiatric teams can start their intervention and follow–up together with the backup of other practitioners, including the patient's family physicians. As we find that FND and PNES might have comorbid neurodiversity (autism, alexithymia and ADHD) and BPD, psychological interventions should accompany psychopharmacological treatment. We had good results with a combination of mood stabilizers, low doses of antide-pressants, and low doses or antipsychotics.[68]

One limitation of the review is the partial number of experimental studies with control groups extractable from the literature which has reduced the power of evidence to a maximum of moderate and many low. Another limitation is that some studies were based on retrospective analysis of cases or from the scrutiny of existing clinical data or interviews. Instead, when more objective investigations (eg vEEG) were used it was easier for the clinicians to confirm the diagnosis of PNES. In our experience, the diagnoses and understanding of triggers can benefit from ethnographic unobtrusive and prolonged observations of patients with FND and PNES in psychiatric and medical wards.

Another research indicates that baseline characteristics, including younger age at diagnosis, a brief duration of PNES before diagnosis, job status, prospective cohabitation, and less comorbid pathologies (such as migraine and anxiety), may serve as predictions for improvement in PNES.[69] In a cohort study, about 50% of patients reported a decrease and 33% a resolution of PNES after e median of 3.3 years from diagnosis.[69]

Abbreviations

FND, Functional Neurological Disorder; PNES, Psychogenic Non–Epileptic Seizure; PTSD, Post–Traumatic Stress Disorder; ADHD, Attention Deficit and Hyperactive Disorder; BPD, Borderline Personality Disorder; OCD, Obsessive Compulsive Disorder; BPAD, Bipolar Affective Disorder; ASD, Autism Spectrum Disorder; EEG, Electroencephalogram; vEEG, visual EEG.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version published; have agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no conflicts of interest in the conduction, completion and dissemination of the current review.

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