

Seizure Disorders and Non-Epileptic Seizures

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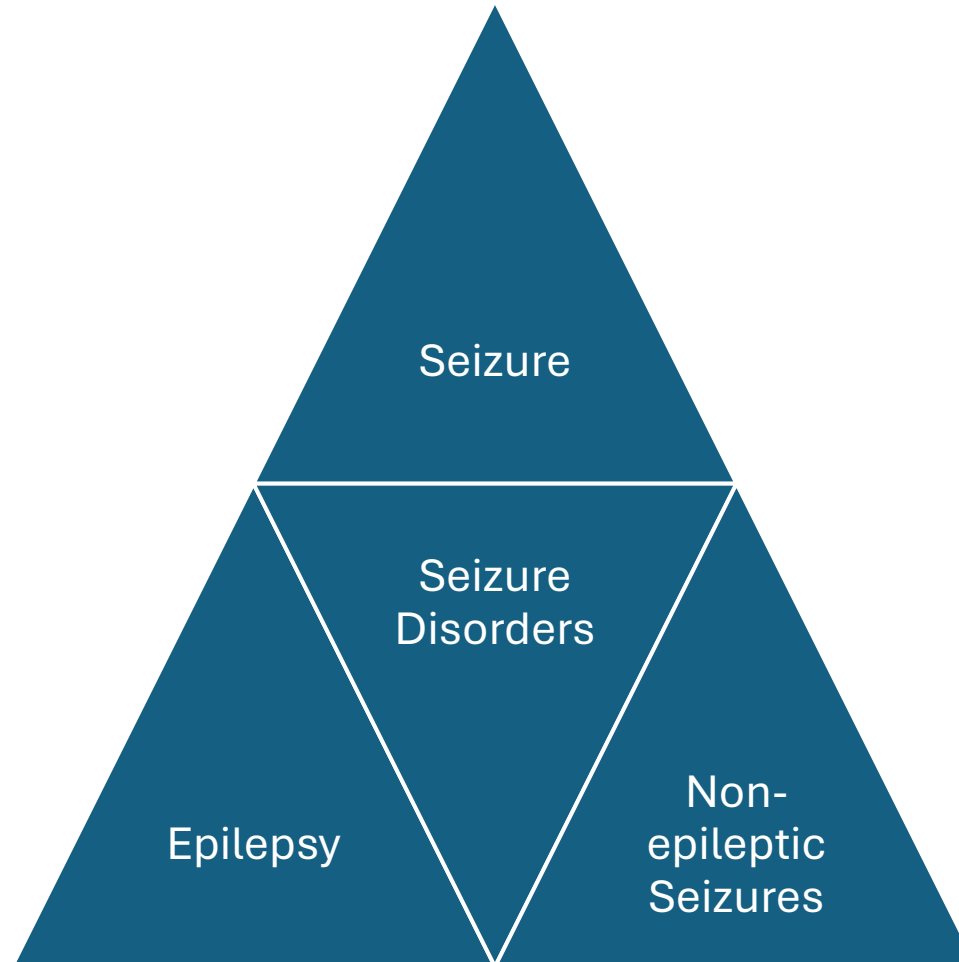
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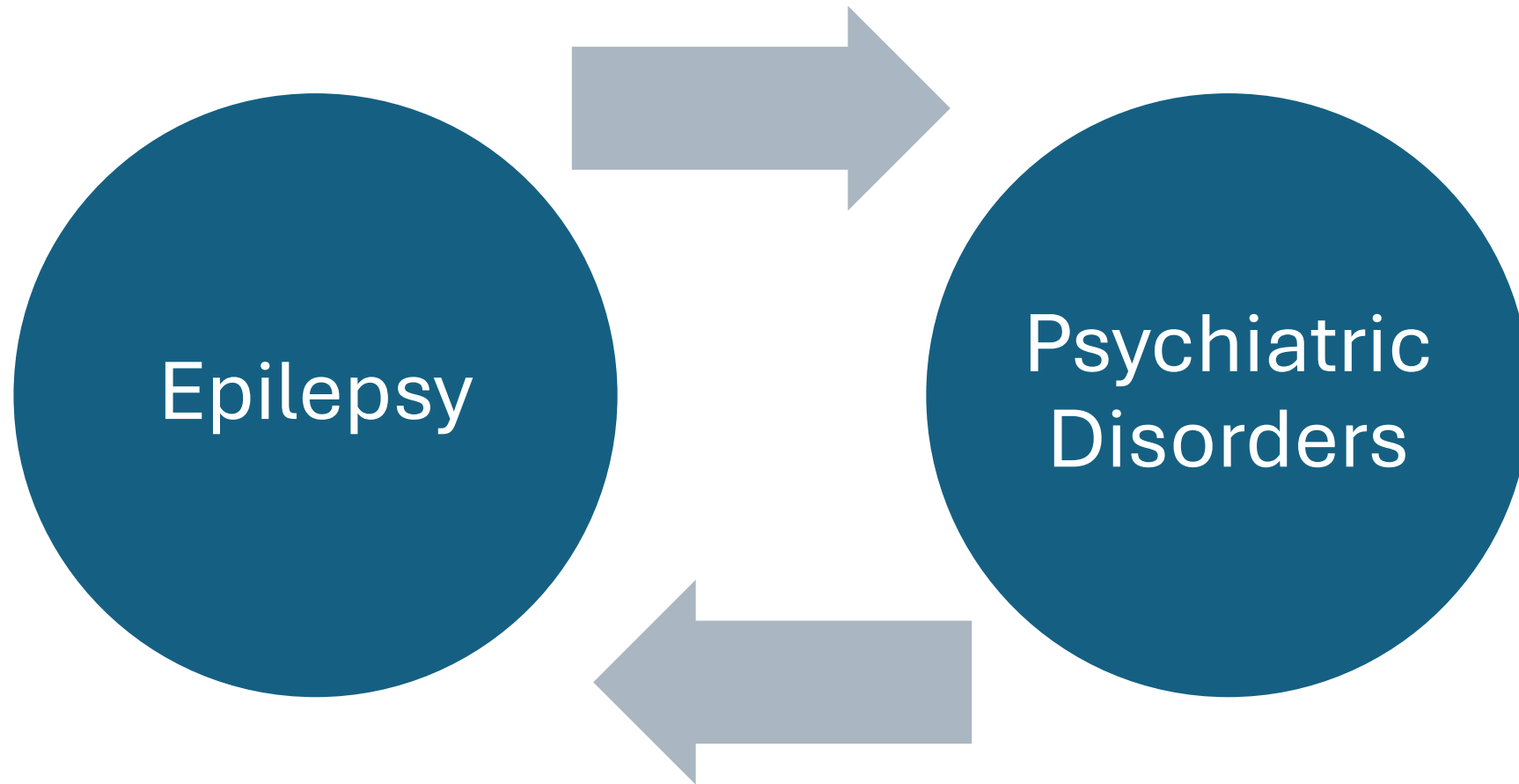
“Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose.”

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Definitions

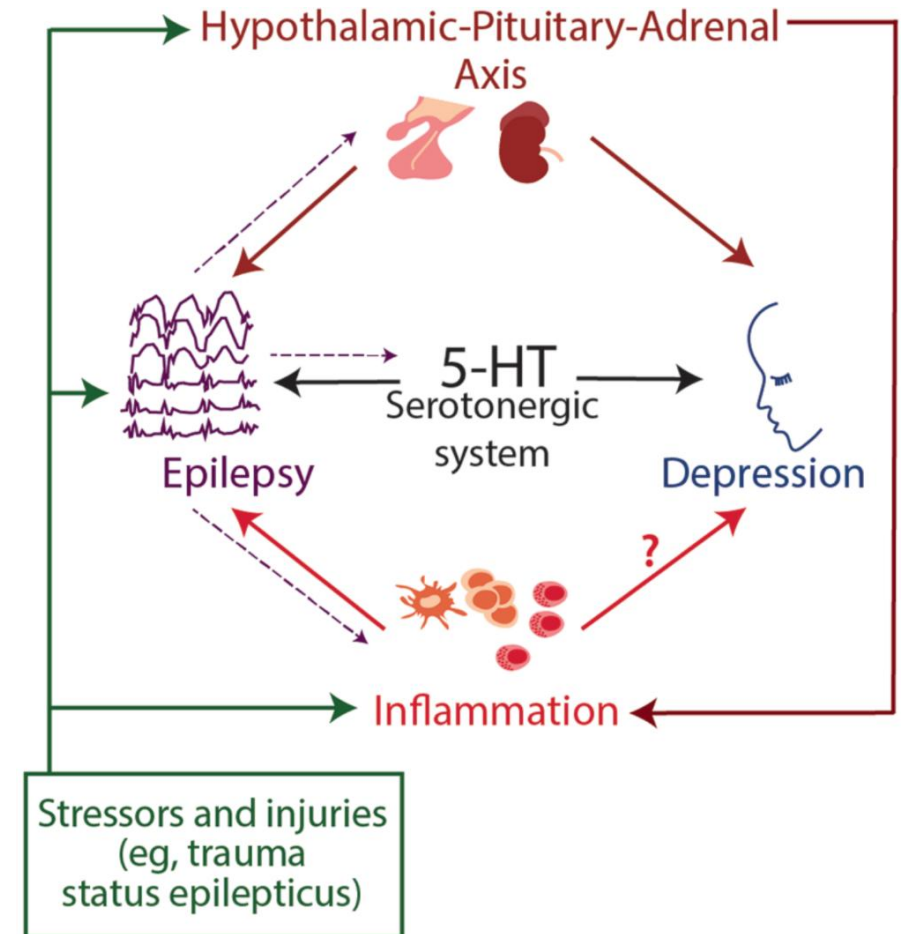


Bidirectional Relationship

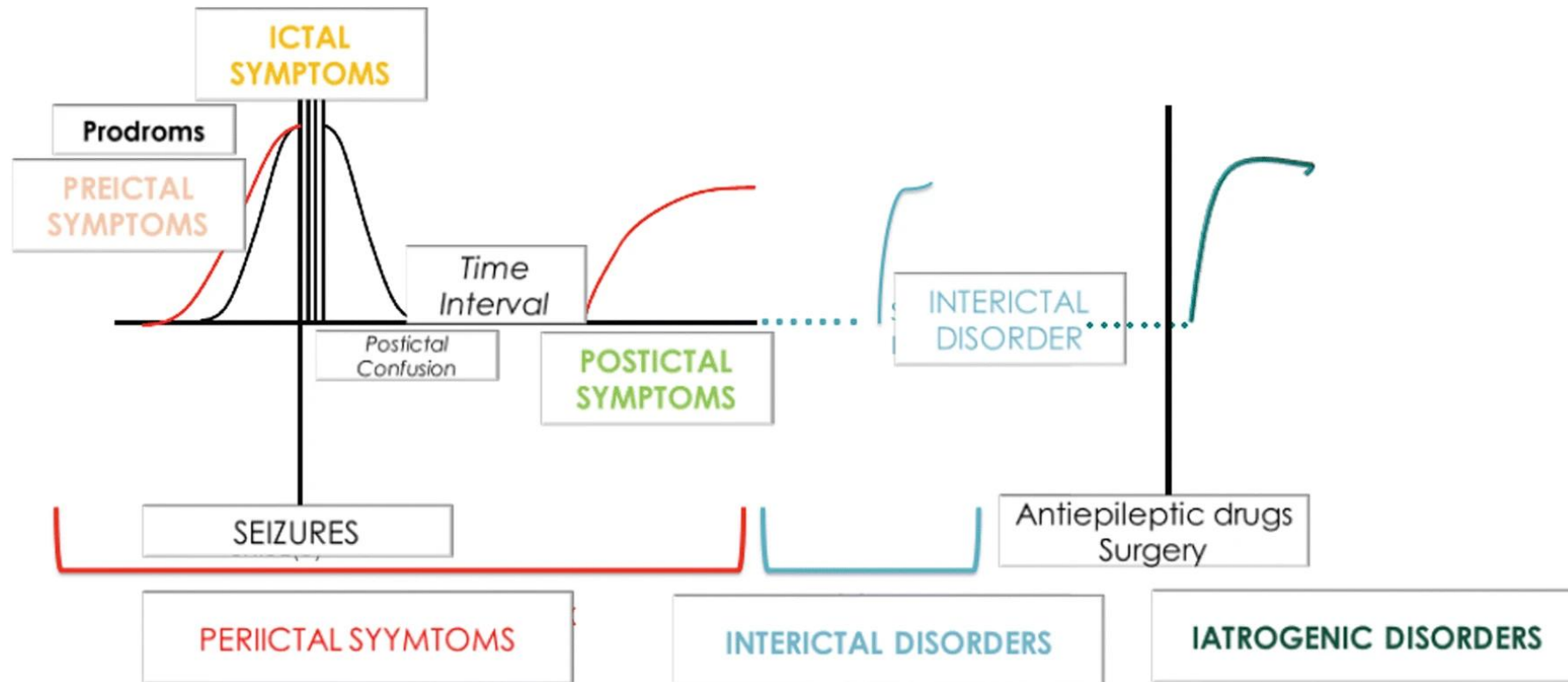


Bidirectional Theories

- Neurotransmitter Disturbance
 - Decreased serotonergic activity
 - Decreased GABA activity
 - Increased glutamatergic activity
- Hyperactive HPA Axis
- Heightened inflammatory response



Symptom Timing



Hingray, C., McGonigal, A., Kotwas, I. *et al.* The Relationship Between Epilepsy and Anxiety Disorders. *Curr Psychiatry Rep* **21**, 40 (2019). <https://doi-org.treadwell.idm.oclc.org/10.1007/s11920-019-1029-9>

Potential Psychotropic Effects of Antiepileptic Drugs

Antiepileptic Drug	Beneficial Effects	Harmful Effects
Barbiturates	Anxiety, mood stabilizing, sleep	Aggression, impaired cognition and attention, depression, irritability, sexual function and desire
Carbamazepine	Aggression, mania, mood stabilizing [±]	Irritability, impaired attention
Ethosuximide		Aggression, confusion, depression, insomnia
Gabapentin	Anxiety, insomnia, social phobia, [±] mood stabilizing	Irritability/agitation (usually in children with disabilities)
Lamotrigine	Depression, [±] mood stabilization, [±] mania [±]	Insomnia, irritability (usually in children with disabilities)
Levetiracetam	Data not available	Anxiety, depression, irritability (all appear more common in children)
Phenytoin	Mania	Depression, impaired attention
Tiagabine	Mania, mood stabilization	Depression, irritability
Topiramate	Binge eating, mania, mood stabilization	Depression, impaired cognition (word finding, memory) and attention, irritability
Valproate	Agitation, aggression, irritability, mania, [±] mood stabilization [±]	Depression
Zonisamide	Mania	Aggression, emotional lability, irritability

Nadkarni S, Devinsky O. Psychotropic Effects of Antiepileptic Drugs. *Epilepsy* Currently. 2005 Sep; 5(5):176-181. doi: [10.1111/j.1535-7511.2005.00056.x](https://doi.org/10.1111/j.1535-7511.2005.00056.x)

Psychotropic Meds in Epilepsy



1. Introduction

Neurologists and epilepsy specialists increasingly find themselves prescribing psychotropic medications to manage common mental health comorbidities in people with epilepsy (PWE) [1–5]. Additionally, PWE may be prescribed psychotropic medications by other non-neurology clinicians, and therefore neurologists need to be aware of relevant implications [6]. For instance, there are substantial potential interactions between antiseizure medications and psychotropic medications, and many antiseizure medications have adverse or beneficial psychotropic properties [7–9]. It is therefore important for neurologists managing

people with epilepsy to have ready access to information summarizing dosing and other key properties of various psychotropic medications. While the various case-based articles in this special issue [10–19] outline detailed information on two appropriate psychotropic medications for each clinical scenario to equip neurologists with practical information enabling appropriate prescribing in similar clinical scenarios, many commonly used psychotropic medications are not covered. The purpose of this final article of the special issue is to provide summary reference information accessible to neurologists, encompassing a broader range of antidepressants, stimulants and antipsychotics, and thus supplement the focused, practical tips in the other articles. Dosing,

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Medication Class	Preferred / Low Seizure Risk	Use with Caution	Higher Seizure Risk / Avoid if Possible	Key Pearls
SSRIs	Sertraline, Escitalopram, Citalopram, Fluoxetine	—	—	First-line for depression/anxiety in epilepsy
SNRIs	Duloxetine, Venlafaxine	—	—	Good options, especially with comorbid pain
Other Antidepressants	Mirtazapine, Trazodone	—	Bupropion , Clomipramine, high-dose TCAs	Bupropion has the greatest seizure risk among commonly prescribed antidepressants
Antipsychotics	Haloperidol, Risperidone, Aripiprazole, Ziprasidone	Olanzapine, Quetiapine	Clozapine , Chlorpromazine	Clozapine risk is dose dependent
Mood Stabilizers	Lamotrigine, Valproate*, Carbamazepine, Oxcarbazepine	Lithium (safe therapeutically, toxic levels increase seizure risk)	—	Many are also antiseizure medications
Benzodiazepines	Lorazepam, Clonazepam, Diazepam	Long-term tolerance	Abrupt withdrawal	Benzodiazepines are anticonvulsants
ADHD Medications	Methylphenidate, Amphetamine formulations, Atomoxetine, Guanfacine	Monitor seizure control	—	Generally safe in well-controlled epilepsy
Anxiolytics	Buspirone, Hydroxyzine	—	—	Minimal effect on seizure threshold
Sleep Agents	Melatonin, Low-dose trazodone, Low-dose doxepin	Chronic sedative use	Abrupt sedative withdrawal	Sleep optimization itself improves seizure control

CYP450 Isoenzyme		
Moderate to Potent Inhibitors	Substrate (most significantly eliminated by isoenzyme)	Moderate to Potent Inducers
CYP1A2		
Fluvoxamine	Asenapine Carbamazepine Clomipramine Clozapine Duloxetine Fluvoxamine Olanzapine	Carbamazepine Phenobarbital Phenytoin Primidone
CYP2C9		
Fluoxetine Fluvoxamine Valproic acid	Amitriptyline Doxepin Fluoxetine Phenobarbital Phenytoin Primidone Valproic acid	Carbamazepine Phenobarbital Phenytoin Primidone
CYP2C19		
Cenobamate Eslicarbazepine Felbamate Fluoxetine Fluvoxamine Oxcarbazepine Topiramate	Amitriptyline Atomoxetine Brivaracetam Citalopram Clobazam Clomipramine Doxepin Escitalopram Imipramine Lacosamide Phenobarbital Phenytoin Primidone Topiramate Valproic acid Venlafaxine Vilazodone	Carbamazepine Phenobarbital Phenytoin Primidone
CYP3A4		
Fluoxetine Fluvoxamine	Aripiprazole Brexiprazole Buspirone Carbamazepine Clobazam Ethosuximide Felbamate Haloperidol Lurasidone Mirtazapine Perampanel Pimavanserin Quetiapine Reboxetine Risperidone Tiagabine Trazodone Venlafaxine Vilazodone Zolpidem Zonisamide	Cenobamate Eslicarbazepine Carbamazepine Oxcarbazepine Phenobarbital Phenytoin Primidone
CYP2B6		
	Bupropion Sertraline	Carbamazepine Cenobamate Phenobarbital Phenytoin Primidone

Adapted from: McMurray HM, Baslet G, de Araujo Filho GM, Dunn D, Kanner AM. *Epilepsy & Behavior Reports*. 2025;30:100760.

Drug Interactions

Antiseizure Medication

Carbamazepine

Phenytoin

Phenobarbital/Primidone

Valproate

Lamotrigine

Effect on Psychotropics

↓ SSRI, SNRI, antipsychotic, and lamotrigine levels

↓ Many psychotropic levels

↓ Many psychotropic levels

↑ Lamotrigine levels; may ↑ antipsychotic adverse effects

Estrogen-containing contraceptives ↓ lamotrigine levels

Clinical Pearl

Strong CYP inducer; many interactions

Enzyme inducer; monitor efficacy

Similar interaction profile

Lamotrigine requires slow titration

May require dose adjustment

High Risk

Bupropion

Clozapine

Clomipramine

High-dose TCAs

Chlorpromazine

Lower Risk

SSRIs

SNRIs

Mirtazapine

Risperidone

Aripiprazole

Haloperidol

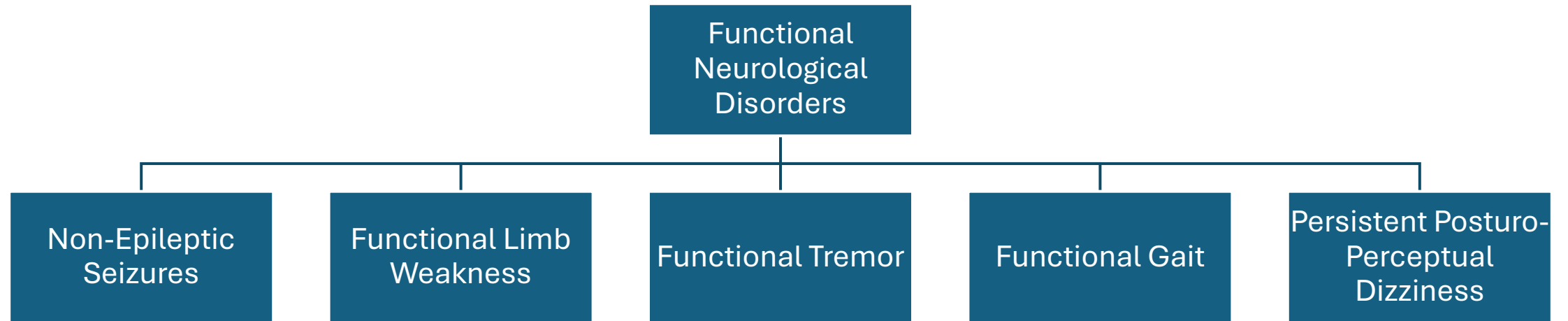
	Lower likelihood	Higher likelihood
Psychiatric/behavioral side effects	Carbamazepine	Brivaracetam
	Lacosamide	Clobazam
	Lamotrigine	Levetiracetam
	Eslicarbazepine	Perampanel
	Gabapentin	Phenobarbital
	Oxcarbazepine	Topiramate
	Pregabalin	Vigabatrin
	Valproic acid	Zonisamide
Cognitive side effects	Brivaracetam	Phenobarbital
	Eslicarbazepine	Primidone
	Gabapentin	Topiramate
	Lacosamide	Zonisamide
	Lamotrigine	Oxcarbazepine
	Levetiracetam	
	Perampanel	
	Pregabalin	
	Rufinamide	
	Tiagabine	
	Vigabatrin	

Adapted from: McMurray HM, Baslet G, de Araujo Filho GM, Dunn D, Kanner AM. *Epilepsy & Behavior Reports*. 2025;30:100760.

Nonpharmacologic Treatment

- Psychoeducation
- Psychotherapy
 - Cognitive Behavioral Therapy
 - Mindfulness Based Therapy
- Neuromodulation
 - Vagus nerve stimulation (VNS)
 - Deep brain stimulation (DBS)
- Surgery

Non-Epileptic Seizures



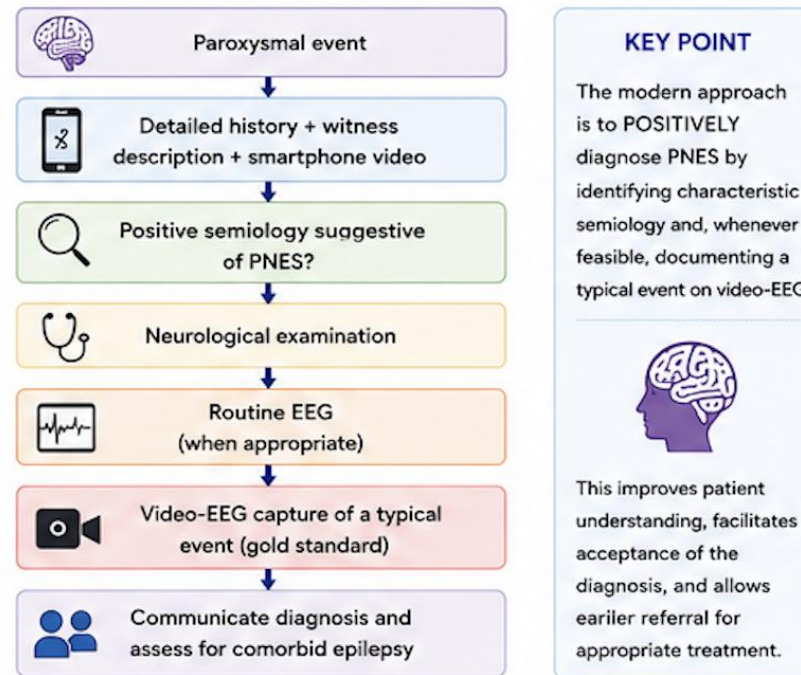
Semiology

Feature	Suggests PNES	Suggests Epileptic Seizure
Onset	Gradual, fluctuating	Sudden
Duration	Often >2–3 minutes	Usually <2 minutes (except status)
Course	Waxing and waning	Stereotyped progression
Motor movements	Asynchronous, variable amplitude	Rhythmic, stereotyped
Limb movements	Side-to-side, out-of-phase	Bilaterally synchronous tonic-clonic
Pelvic thrusting	Common, often prolonged	Can occur (especially frontal lobe epilepsy), usually brief
Head movements	Side-to-side shaking	Less common
Eye closure	Eyes tightly closed, resistance to opening	Eyes usually open at onset
Eyelid flutter	Common	Less common
Vocalization	Crying, screaming, talking during event	Ictal cry usually only at onset of generalized tonic-clonic seizure
Responsiveness	Partial awareness or fluctuating responsiveness	Usually impaired throughout focal impaired awareness or generalized seizures
Memory	Recall of parts of event common	Usually amnesia if awareness impaired
Postictal state	Minimal confusion, rapid recovery	Confusion, fatigue, headache common
Injuries	Less common	Tongue biting, fractures, serious injury more common
Tongue biting	Tip of tongue	Lateral tongue more specific
Incontinence	Can occur	Can occur

Diagnosis

1 How to Diagnose PNES (Psychogenic Non-Epileptic Seizures)

*A positive diagnosis based on clinical
features and video-EEG*



Diagnosis

2

1. History

The history often provides the strongest clues.



Ask about:

- Onset and offset
- Duration
- Frequency
- Triggers
- Awareness
- Motor behaviors
- Vocalizations
- Eyes open or closed
- Injuries
- Tongue biting
- Incontinence
- Recovery

Context:

- Stressful life events
- Medical illness
- Psychiatric history
- Trauma (not required)
- Chronic pain, migraine
- Functional symptoms elsewhere

TIP

Obtain witness description or smartphone video when available. These are extremely valuable.



Diagnosis

3

2. Positive Clinical Signs

Features suggestive of PNES include:

- ✓ Long duration (>2–3 minutes)
- ✓ Fluctuating course
- ✓ Waxing and waning intensity
- ✓ Asynchronous limb movements
- ✓ Side-to-side head shaking
- ✓ Eyes tightly closed
- ✓ Resistance to eye opening
- ✓ Crying during the event
- ✓ Recall of portions of the event
- ✓ Minimal postictal confusion
- ✓ Symptoms improving with distraction

No single feature
is diagnostic;
combinations
are more
informative.



Remember

Some features (e.g.,
incontinence, injury,
pelvic thrusting) can
also occur in
epileptic seizures.

Diagnosis

4

3. Neurological Examination & 4. EEG

Neurological Examination

Examination between events.

Also assess for other functional neurological signs:



- Hoover sign
- Tremor entrainment
- Functional gait findings
- Give-way weakness
- Inconsistency across examination

The presence of other functional neurological signs increases the likelihood of FND but does not establish PNES.

EEG

Routine EEG

- Usually does NOT diagnose PNES
- A normal routine EEG does NOT exclude epilepsy
- Does NOT confirm PNES



Video-EEG (Gold Standard)

The diagnostic gold standard is capture of a typical clinical event on simultaneous video-EEG showing no ictal epileptiform activity, with semiology consistent with PNES.

Video-EEG correlates:

- Clinical behavior
- EEG activity
- Awareness
- Event evolution



Diagnosis

5. Diagnostic Certainty (ILAE Framework) & 6. Important Differential Diagnoses

Level	Basis
Possible PNES	History consistent with PNES and normal interictal EEG
Probable PNES	Typical event witnessed by an experienced clinician with compatible semiology
Clinically established PNES	Typical event observed with supportive neurological assessment and no evidence of epilepsy
Documented PNES (Gold Standard)	Typical event captured on video-EEG with absence of ictal epileptiform activity

6. Important Differential Diagnoses



Always consider alternative or coexisting diagnoses.
Coexisting epilepsy occurs in ~10–30% of patients with PNES.

Diagnosis

6 7. Laboratory Testing & 8–9. Key Points

7. Laboratory Testing

Test	Role
Serum prolactin	May rise after generalized tonic-clonic or some focal impaired-awareness seizures, but cannot reliably distinguish PNES from all epileptic seizures and is NOT recommended as a stand-alone diagnostic test.
CK	Limited usefulness
Lactate	Poor specificity
Serum ammonia	Not routinely recommended

8. Coexisting Epilepsy

10–30% of patients with PNES have coexisting epileptic seizures.

Consider coexisting epilepsy if:

- Events are not all stereotyped
- Some episodes occur exclusively from sleep
- There are injuries or lateral tongue biting with certain events
- EEG or imaging suggests epilepsy

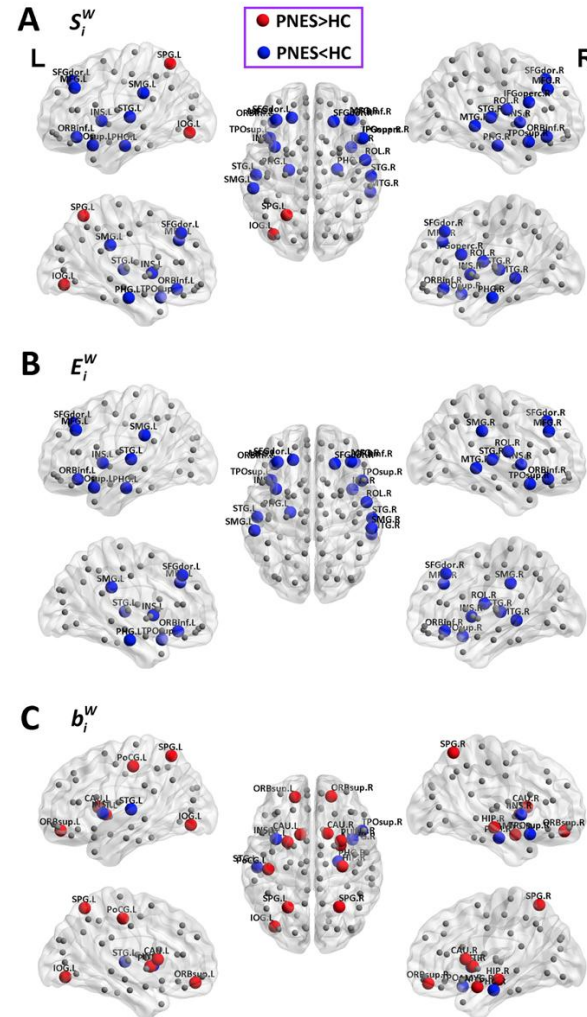


Patients may have more than one seizure type, and each should be characterized separately.

9. Practical Diagnostic Algorithm

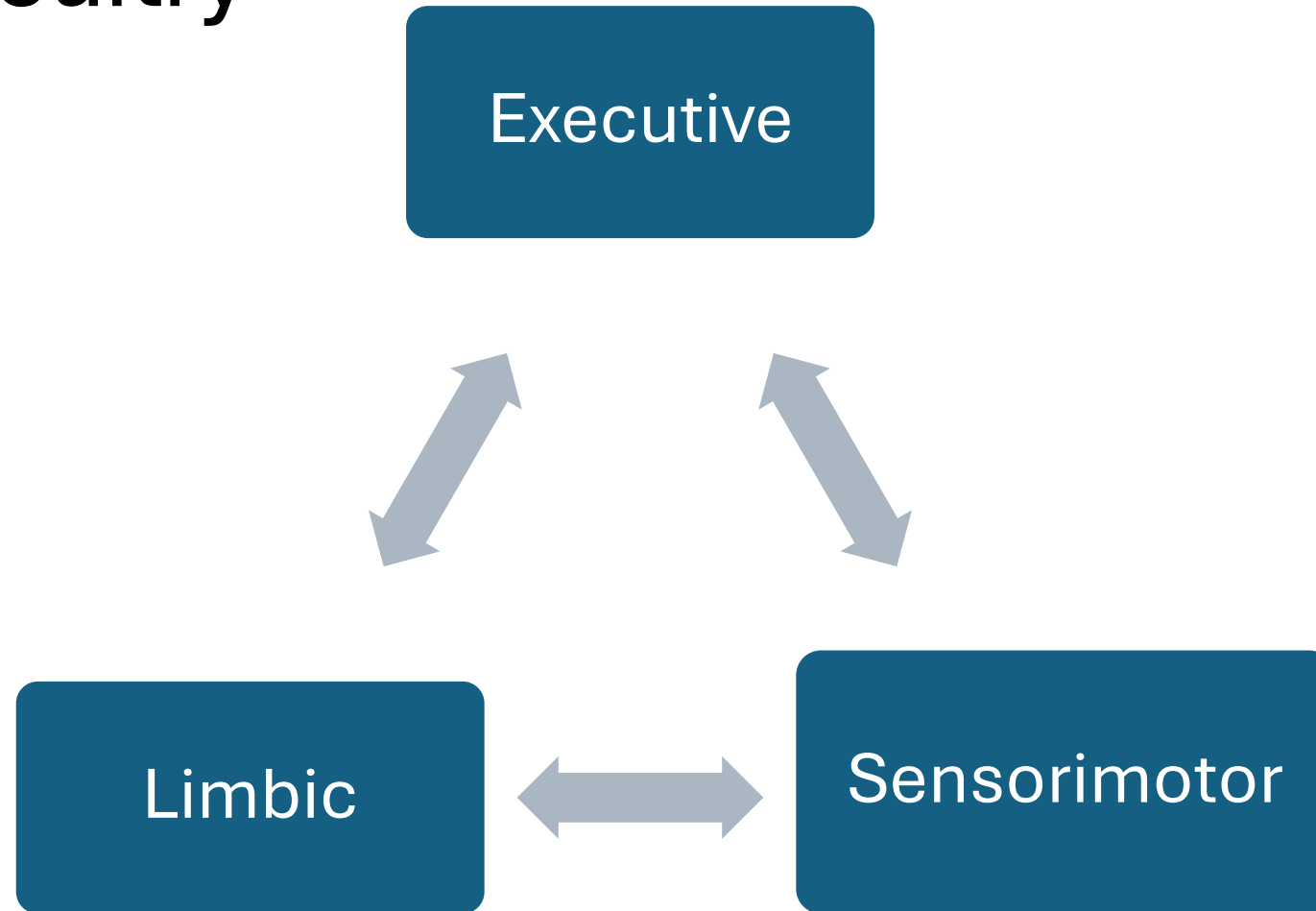


Neuroimaging

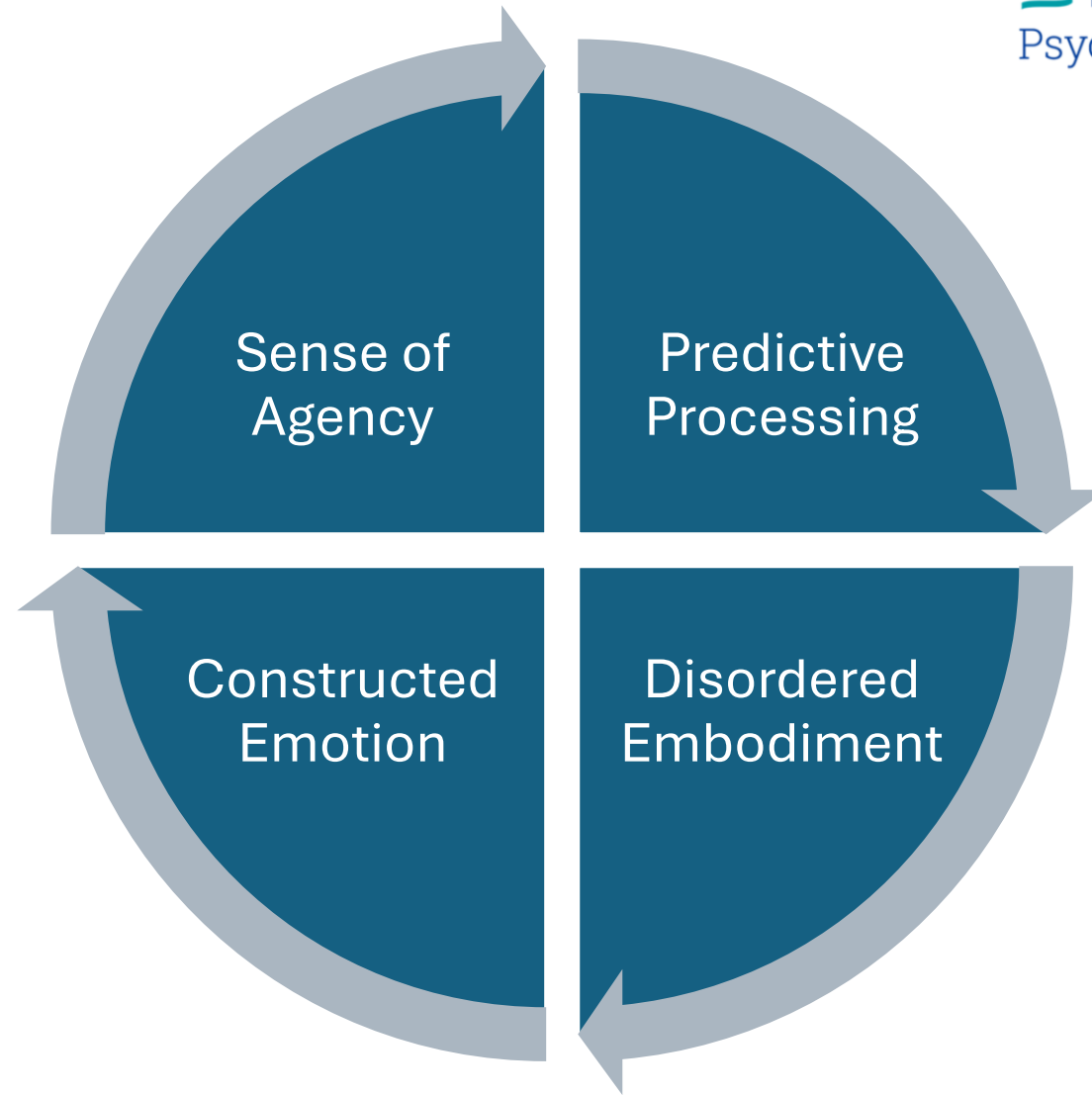


Ding JR, An D, Liao W, Li J, Wu GR, Xu Q, Long Z, Gong Q, Zhou D, Sporns O, Chen H. Altered functional and structural connectivity networks in psychogenic non-epileptic seizures. PLoS One. 2013 May 22;8(5):e63850. doi: 10.1371/journal.pone.0063850. PMID: 23717498; PMCID: PMC3661726.

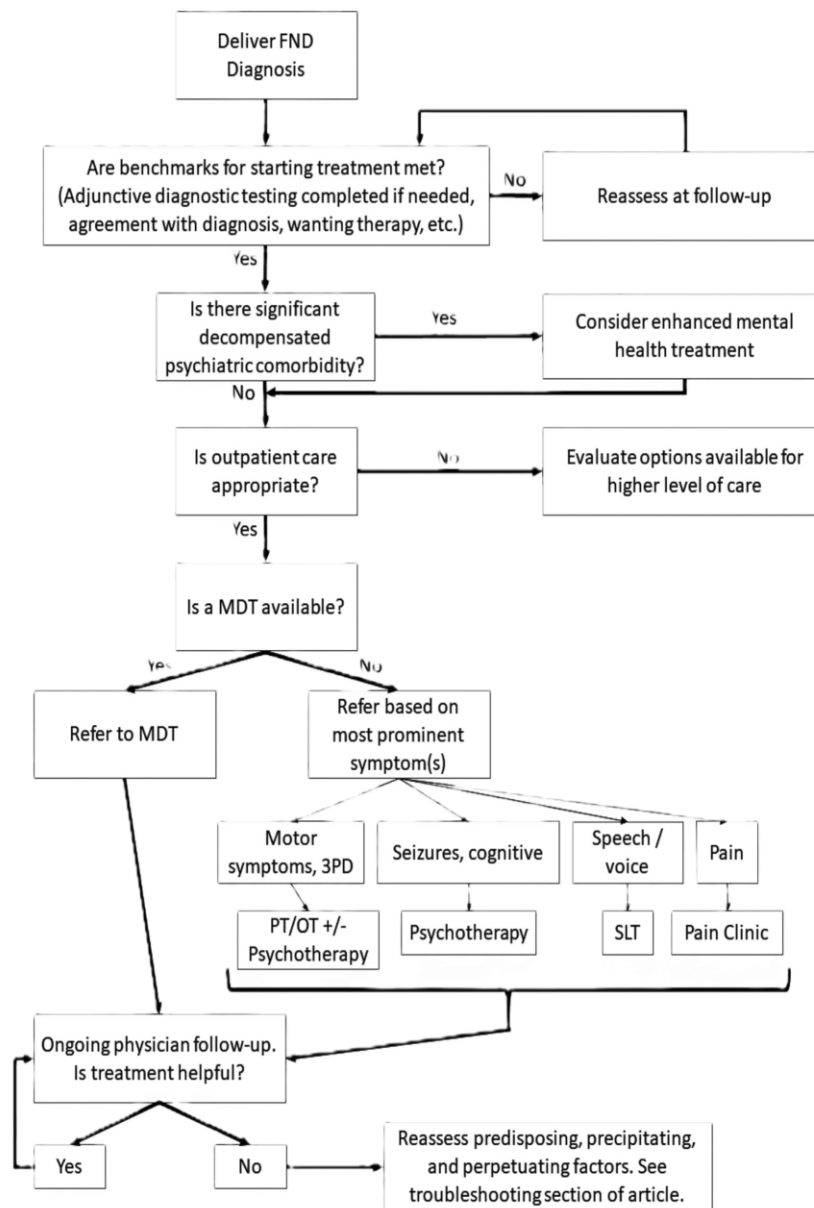
Neurocircuitry



Theories



Treatment Approach



Finkelstein SA, Adams C, Tuttle M, Saxena A, Perez DL.
Neuropsychiatric Treatment Approaches for Functional
Neurological Disorder: A How to Guide. Semin Neurol. 2022
Apr;42(2):204-224. doi: 10.1055/s-0042-1742773. Epub 2022
Feb 21. PMID: 35189644.

Resources

- [Neurosymptoms.org](https://neurosymptoms.org)
- FND Hope
- Overcoming Functional Neurological Symptoms by Christopher Williams et al
- Neurology Podcast
- Multidisciplinary Clinics