

Treatment of functional neurological disorder: current state, future directions, and a research agenda

Review

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Abstract

Functional neurological disorder (FND) encompasses a complex and heterogeneous group of neuropsychiatric syndromes commonly encountered in clinical practice. Patients with FND may present with a myriad of neurological symptoms and frequently have comorbid medical, neurological, and psychiatric disorders. Over the past decade, important advances have been made in understanding the pathophysiology of FND within a biopsychosocial framework. Many challenges remain in addressing the stigma associated with this diagnosis, refining diagnostic criteria, and providing access to evidence-based treatments. This paper outlines FND treatment approaches, emphasizing the importance of respectful communication and comprehensive explanation of the diagnosis to patients, as critical first step to enhance engagement, adherence, self-agency, and treatment outcomes. We then focus on a brief review of evidence-based treatments for psychogenic non-epileptic seizures and functional movement disorder, a guide for designing future treatment trials for FND, and a proposal for a treatment research agenda, in order to aid in advancing the field to develop and implement treatments for patients with FND.

Introduction

Functional neurological disorder (FND), also known as conversion disorder, is a heterogeneous group of syndromes that commonly present to neurologists, primary care clinicians, psychiatrists, and emergency departments. The most common variants are functional seizure disorder (psychogenic non-epileptic seizures [PNES]), functional movement disorder (FMD), and functional cognitive disorder. Patients with FND tend to be high utilizers of health care resources due to diagnostic challenges, problems with access to treatment, and care coordination. Evidence-based treatments for FND exist, and more are being developed and need to be developed, that are seeking symptom resolution and improvement in quality of life.¹ While effective treatments are available, lack of awareness of FND among health care professionals and in the community remain significant problems and a barrier towards treatment.² Many times, FND is persistent and chronic, and factors determining long-term outcomes are incompletely understood.³ Given the prevalent and disabling nature of this common disorder, the rationale of this paper is to describe current approaches to FND treatment for the non-specialist, and to define a research agenda to advance available treatment modalities for the clinical and research communities. Didactic and explanatory illustrations of treatment approaches are described and provided in figures in this article.

Approach to FND Treatment: Delivery of Diagnosis as the First Step

Accurate diagnosis is the first step in the treatment of FND and relies predominantly on a clinician obtaining a comprehensive medical, neurological, and psychiatric history and examination. Identification of “positive signs,” that is, recognition of neurological examination findings that are incongruent with other neurologic disorders have been emphasized in DSM-5, has shifted clinician’s abilities from a hedging a diagnosis of exclusion, now making FND a diagnosis of inclusion.⁴ Positive exam signs, such as Hoover’s sign, entrainment, and tubular vision defect are well described in other reviews¹ and are covered elsewhere in this issue.

Delivery of the diagnosis should occur in a positive, non-judgmental, non-pejorative, and clear manner.⁵ FND needs to be understood within a biopsychosocial, spiritual, and cultural framework that informs the treatment (an approach to which is described below). Although FND is not associated with classical structural brain lesions, evolving research is demonstrating

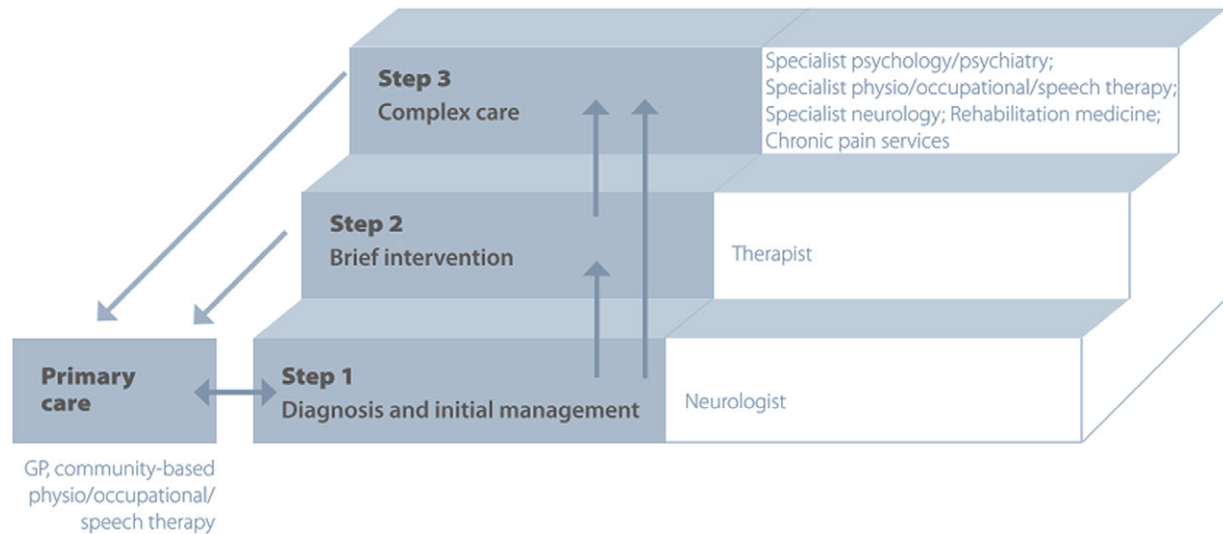


Figure 1. Proposed model of stepped care for FND (adapted from Carson and Stone, NHS Scotland, 2014).⁹

evidence for neural circuitry dysfunction in limbic and sensorimotor pathways. Providing an explanatory model to patients that addresses individual risk factors and triggers and outlining an individualized treatment path with emphasis on the potential reversibility of symptoms will aid in forming a therapeutic partnership. Motivational interviewing was recently studied and found to improve treatment adherence and outcomes in patients with PNES.⁶ Explaining that the good news is that treatments exist for the symptoms may provide hope to patients with FND and their families, many of whom have been discouraged by the lack of resources and receptive practices for their condition.

Application of Treatment Models

Different treatment modalities may have variable benefits in different patient groups, depending on individually contributing factors toward pathophysiology. Clear communication in planning and treatment delivery and continuity of care among healthcare professionals is key to treatment success. Assessment of patients in specialized FND and neuropsychiatric clinics allows for dedicated patient education and treatment planning.^{7,8} In addition to addressing the “core symptoms” of FND, integrating addressing common comorbidities in the treatment plan, including chronic pain and fatigue is important. Patients with predominant pain may be advised to undergo a pain rehabilitation program along with, or prior to, focusing on other FND symptoms, and other medical and neurological comorbidities may need to be addressed separately, as well. Important goals of treating patients with FND are maximizing functional independence, regaining control, and self-agency. Components of treatment may include classic psychotherapeutic modalities, rehabilitation interventions, and addressing comorbidities. Regardless of the specific intervention, development of a trusting clinician/patient rapport is crucial in order for patients to feel heard and understood and not alone in the process, and help diminish feelings of shame, guilt, and distress.

Within a stepped model of care as initially proposed by Carson and Stone,⁹ individual treatment is tailored to the needs of each patient based on symptom severity (Figure 1) and complexity to optimize resource allocation. Patients with mild or transient symptoms are provided education and advice by the neurologist making

the diagnosis and referred back to primary care (Step 1). Patients with more severe symptoms but without complex psychiatric comorbidities may benefit from a brief psychotherapeutic or rehabilitation intervention with a physical, occupational, or speech therapist (Step 2). Patients with complex symptom presentations, a high level of disability and comorbidities and those who have failed prior treatment interventions are likely to benefit from specialized multidisciplinary FND therapy delivered in an outpatient, day hospital, or inpatient setting (Step 3). Depending on individual symptoms and comorbidities, the treatment team may involve a neurologist, psychiatrist, (neuro)psychologist, physiatrist, physical, occupational, and speech therapist, clinical social worker, mental health clinician, and others (Figure 2). Involvement of the patient’s family in psychoeducation and therapy is important to ensure transfer of treatment success to the home environment and prevention of relapses. We will review some of the evidence-based treatments from the literature for PNES and FMD, as examples of multi-modal therapeutic approaches.

Treatment of Functional Seizures/PNES

General treatment principles for PNES include psychoeducation to facilitate understanding and acceptance of the diagnosis, addressing predisposing, precipitating, and perpetuating factors¹¹ within a biopsychosocial spiritual (BPSS) framework, which are queried in the developmental and social history, as well as addressing medical and psychiatric comorbidities. Patients will learn to identify seizure triggers and apply techniques such as action planning, mindfulness, and grounding to reduce seizure frequency and change maladaptive behavioral patterns. Many therapists work with methods based on conventional cognitive behavioral therapy (CBT),¹² psychoeducation,¹³ acceptance commitment therapy,¹⁴ dialectical behavior therapy,¹⁵ psychodynamic,¹⁶ and narrative therapy¹⁷ to address current stressors, past trauma, and relational issues. Involvement of family in treatment, addressing relationships, work life, and social connectedness are important for treatment success.¹⁸

LaFrance and colleagues have designed, tested, and implemented a multi-modality, Beckian-based,^{19,20} CBT-informed psychotherapy,²¹ described as Neurobehavioral Therapy (NBT),

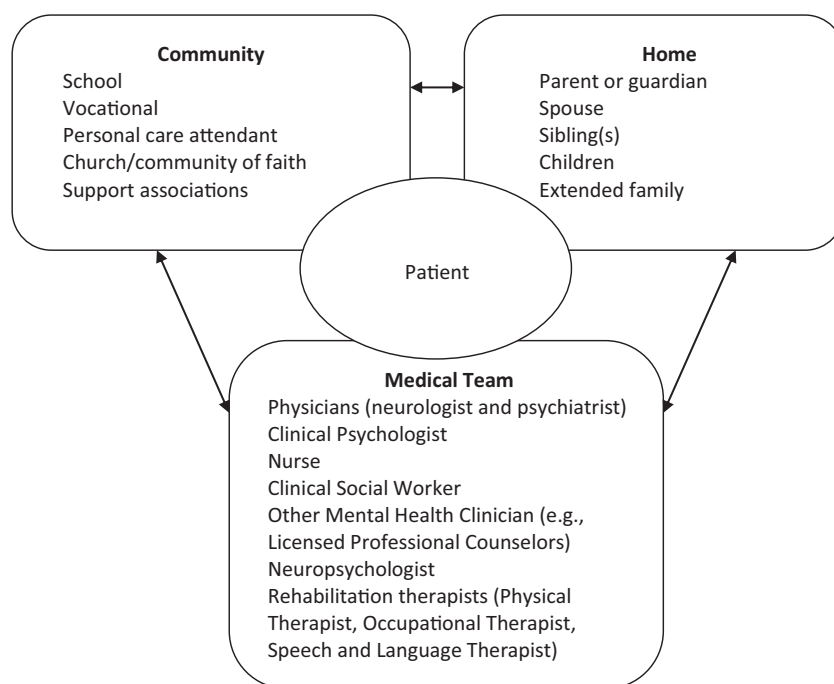


Figure 2. Patient-centered systems model for PNES (modified from LaFrance and Devinsky, 2004, with permission from John Wiley and Sons).¹⁰

which is structured, time-limited, short-term, and present-oriented. The intervention is built on the assumption that life experiences and trauma in patients with PNES result in maladaptive core beliefs (negative schemas), cognitive distortions, and somatic symptoms. The 12, 1 hour long, individual therapy sessions are specifically tailored for known pathologies in patients with PNES in order to address both the seizures *and* the comorbidities that commonly occur in this disorder, and promote behavioral change, self-control, and self-efficacy (see Table 1 for sessions, targets, and modalities). The goal of treatment is to equip patients to assume control over their seizures; contextualizing the individual's environment; identifying moods, situations, and thoughts; training healthy communication and support seeking; understanding central nervous system medications and seizures; conducting a functional behavioral analysis; learning relaxation techniques; examining external stressors and internal triggers; and preparing for life after completing the time-limited intervention.

Summary of psychotherapeutic modalities in each chapter of Reiter et al²¹ (reproduced with permission of The Licensor through PLSclear; in LaFrance Jr WC, Schachter SC, eds., *Gates and Rowan's Nonepileptic Seizures*, New York: Cambridge University Press, 2018, p. 302).

Case illustrations of how to conceptualize the BPSS and cultural aspects in the patient formulation are given in clinical vignettes and clinician interactions in the therapy training manual,²² which is used to facilitate the standardized, manual-based delivery.²¹ An example of the formulation would include relevant data on birth, developmental, trauma/abuse, education, relationships in family of origin and extended family, work, avocation, military, legal, religion/faith history, derived from the patient and from accompanying family member/significant other, if present.

In the open label²³ and pilot randomized controlled trial (RCT) studies,²⁴ therapy was administered according to the manual-based protocol devised and modified by LaFrance's research group from

the original Epilepsy Workbook.²⁵ Given that NBT has shown significant reductions in seizures and co-morbidities in two civilian pilot trials, as cited above, and in a study with Veterans with documented PNES,²⁶ it is being used in civilian and Veterans hospital and clinic facilities across the country by trained clinicians, including neurologists/epileptologists, psychiatrists, neuropsychiatrists, psychologists, neuropsychologists, and social workers.²⁷ Clinicians at several VA Epilepsy Centers of Excellence have been trained to deliver NBT, in person and via clinical video telehealth, and service agreements have been established to provide telehealth treatment at VAs around the country.²⁸ As shown in Figure 2, this intervention involves medical, allied health, community, and family resources for management,¹⁰ and addresses the gap of clinician frustration regarding lack of treatments, and provides hope to Veterans with PNES for improvement in seizures, comorbid symptoms, and quality of life.²⁹

Treatment of FMD

Treatment planning in FMD needs to be individualized, taking symptom severity and comorbidities into account. Members of the treatment team may include a neurologist, psychiatrist, (neuro)psychologist, psychiatrist, physical/occupational/speech therapist, and a clinical social worker (see Figure 3). Many patients with FMD can benefit from focused interventions, that may be delivered by a psychologist, physical, occupational, or speech therapist, with the goal of regaining control over movements, identifying trigger factors, and facilitating behavioral changes. One randomized controlled trial showed modest benefit from a guided self-help manual based on CBT principles in a mixed FND patient group.³⁰ A randomized clinical trial tested hypnosis compared to a wait list control in 44 patients with motor conversion disorder, which showed improvement in the hypnosis group.³¹

Table 1. Therapeutic Topics, Targets, and Modalities for Neurobehavioral Therapy Treatment of PNES.

Session	Chapter Title	Target	Psychotherapy Modality
Session intro	<i>Introduction for patients: understanding seizures</i>	Describes epileptic and nonepileptic seizures	Psychoeducation
Session 1	<i>Making the decision to begin the process of taking control</i>	Patient makes the choice to engage in treatment	Motivational interviewing
Session 2	<i>Getting support</i>	Addresses communication styles and goals	Interpersonal therapy
Session 3	<i>Deciding about your medication therapy</i>	Discusses central nervous system medications	Psychoeducation
Session 4	<i>Learning to observe your triggers</i>	Examines physical, internal, and external triggers	CBT schema therapy
Session 5	<i>Channeling negative emotions into productive outlets</i>	Explores emotions, cognitions, and relieving actions	Dialectical behavior therapy
Session 6	<i>Relaxation training</i>	Teaches relaxation techniques	Cognitive behavioral therapy
Session 7	<i>Identifying your pre-seizure aura</i>	Identifies aura using self-awareness techniques	Mindfulness
Session 8	<i>Dealing with external life stresses</i>	Addresses relational and psychosocial stresses	Psychodynamic
Session 9	<i>Dealing with internal issues and conflicts</i>	Examines past trauma and unconscious processes	Psychodynamic
Session 10	<i>Enhancing personal wellness</i>	Sets healthy lifestyle priorities	Self-efficacy/self-management
Session 11	<i>Other seizure symptoms</i>	Describes comorbid symptoms	Mindfulness
Final reading	<i>Taking control: an on-going process</i>	Provides perspective on life after treatment	Acceptance and commitment therapy

Abbreviation: PNES, Psychogenic Non-Epileptic Seizures.

**Figure 3.** Multidisciplinary treatment for FMD.

For patients without significant psychiatric comorbidities or chronic pain, a 5-day specialized physical therapy (PT) treatment protocol led to 72% symptoms improvement at 6 month follow-up in patients with functional motor disorders, compared to only 18%

improvements in the control group.³² The goal of PT for FMD is re-establishing normal movement patterns and learning control over involuntary movements. After education about the diagnosis and establishing a shared treatment plan therapy focuses on goal-directed rehabilitation, using strategies to facilitate automated movement patterns and controlling unwanted movements. Recommendations for PT in FMD have been summarized in a consensus statement in the UK.³³ FMD specific therapy principles include limited “hands-on” treatment, facilitating rather than supporting movements, encouraging early weight bearing, goal-directed rehabilitation focused on function and automatic movement, minimized reinforcement of maladaptive movement patterns and postures, and avoidance of adaptive equipment and mobility aids. Therapy is delivered within a “psychologically-informed” framework, and relaxation and mindfulness training are incorporated into treatment sessions.

For patients with a high degree of disability, treatment in a day hospital or inpatient setting can provide the benefits of an intensive multidisciplinary treatment approach by a specialized team under close monitoring and temporary withdrawal from a potentially maladaptive home environment. In a randomized-controlled trial by Jordbru et al., patients with functional gait disorder admitted to a three-week inpatient rehabilitation program had significant improvement in their ability to walk, higher functional independence and mobility and improved quality of life compared with an untreated control group, and sustained improvements at follow-up after 1 year.³⁴ There is currently no standardized approach to provide inpatient treatment for patients with FMD, although several other retrospective case series have been encouraging.^{8,35} In the motor retraining program developed by LaFaver and colleagues, patients were admitted to a one-week stay in a rehabilitation

hospital, undergoing daily physical, occupational and speech therapy, a total of 5 hours of CBT, guided meditation, and motor imaging training.⁸ Initial and 6-month outcomes showed significant improvements in motor symptoms, with more modest gains in overall quality of life.³⁶ Other treatment programs in the UK take place in psychiatric facilities with longer stays depending on patients' needs.³⁷ Well-designed randomized controlled treatment studies with larger number of patients are needed to optimize treatment allocation and understand factors determining long-term outcomes.

Unmet Needs in FND Treatment

Research agenda

Although many patients achieve treatment benefits with therapies outlined in the previous section, complete symptomatic remissions are rare, and some patients are refractory to currently available therapies despite good motivation and full engagement. The purpose of this section is to outline a research agenda to advance treatment for FND. Clinical experience and studies show that treatment needs to be interdisciplinary and unify experts from many disparate disciplines. A unique challenge is the design and conduct of adequately powered trial for current and future therapies. These challenges are universal, whether we are looking at psychotherapy, neuromodulation trials, or medication trials. In the past, there has been a siloed approach between neurology and psychiatry that might have been prevented more research in this area.

Current and future intervention to be studied include neuro-modulation (eg, transcranial magnetic stimulation,^{38,39}), hypnosis, pharmacological agents (including psychotropics⁴⁰ and psychedelics⁴¹), rehabilitation medicine, placebo interventions,⁴² and different milieu, such as other individual and group therapies.⁴³ In addition to the intervention modality, research questions revolve around frequency and duration, treatment setting (inpatient vs outpatient), individual vs group therapy, combined modalities, and durability of treatment effect and maintenance. There is also a need to explore the value of web-based and telehealth interventions, and the combination of remote and in-person treatments. These challenges are described further below and listed in Table 2.

Future Treatment Interventions: Challenges and Opportunities

Study design challenges

One of the major challenges of designing trials for FND/CD is the comparison arm. Some of the potential options for comparator arms are treatment as usual, weightless control, active comparator arms, placebo-sham control. Elements of the control that must be addressed include time and attention. One unique approach to an innovative control study may involve dismantling an effective treatment into components. This approach allows investigators to determine which components of the accepted treatment are active and whether there is synergy between various components of the intervention.

Methodological challenges in developing trials for FND/CD

One of the major challenges in this area is how one conceptualizes FND—whether one is a “splitter or lumpier.” From a “splitter”

Table 2. Proposed Research Agenda for FND Treatment Studies.

Treatment efficacy
Potential RCTs on single and multidisciplinary interventions
Psychotherapies
Physical therapy
Occupational therapy
Speech therapy
Pharmacotherapy
Hypnosis
Neuromodulation
Comparative efficacy treatment research
Treatment delivery
In-clinic vs remote/online
Individual vs group therapy
Outpatient vs inpatient treatment
Outcome measures
Validation of current outcome measures
Development of FND specific outcome measures
Integration of wearable devices and other technology-assisted outcome measures
Treatment dissemination
Education models for healthcare professionals
Other considerations
Role of acceptance of the diagnosis for treatment outcomes
Role of cultural background (eg, race and socioeconomic factors) on treatment outcomes

Abbreviation: FND, functional neurological disorder; RCTs, randomized clinical trials.

perspective, semiological and comorbidity heterogeneity is a potential problem for research in this population. Patients with FND have a protean range of symptoms and presentations, along with a plethora of psychiatric and somatic comorbidities. In contrast, the “lumper” conceptualization identifies conversion disorder as a unifying factor in most patients with FND, and the phenotypic variations and comorbidities are expected in a symptomatic continuum along a spectrum in this complex population.

Some of the other characteristics that can impact both the adherence and retention in trials include acceptance of the diagnosis, the motivation and readiness to change of the subject, the subject's perception of expectancy, and credibility of the proposed interventions in the trial, and the ability of the patient being able to attend sessions regularly (whether due to transportation or insurance issues).

Characteristics of potential participants that need to be addressed in the inclusion/exclusion impact are dissociation, avoidance behavior, substance use, and disability application/litigation. Proximity to the site and support system can be integral to compliance.

Challenges in outcome measures

The choice of outcome measures depends on the main hypothesis and the intention of the trial. The study may be addressing efficacy

or effectiveness of an acute-phase intervention, long-term effects, or examining cost and utilization. Thus, monitoring the desired outcome may use different measures to determine the treatment impact.

Defining best outcome measures is an area of active research. Common outcome domains and measures in FND intervention studies include: core symptoms, other physical symptoms, psychiatric symptoms, life impact (eg, QOL/disability, general functioning), and health economics/cost-utility, illness beliefs, and attributions.⁴⁴ The importance of the choice of primary and secondary outcome issue was recently demonstrated in the successful completion of the first fully powered psychotherapy RCT for PNES, with benefit in many secondary measures, but a negative primary outcome of difference between conventional CBT and enhanced standard medical care at 12 month follow up,⁴⁵ which may not have been the most representative outcome measure representation of the benefit of CBT for PNES observed in this trial.

Other outcomes may include physiological outcomes, which could be monitored with serologic, genetic, neuroimaging, autonomic measures, and actigraphy. Integration of wearable devices and other technology-assisted devices may facilitate the subjective and objective response in patients' natural environment.

Some other important components of trial design relate to the trial duration and impact, which includes whether the purpose of the trial is to assess acute treatment response, the durability of treatment, or the need for maintenance treatment. Factors to be taken into account include: the length of the acute treatment trial, the frequency of assessment within the trial, the frequency of the intervention delivery, the schedule of follow-up assessments administration, the length of follow-up, and the mechanism of collection of follow up data (eg, pen and paper, electronic survey).

Whether or not to allow for other treatments during and with the active intervention is another consideration for designing efficacy or effectiveness of trials. The potential use of naturalistic follow-up in the untreated population patients using registries or biorepository is another potential comparison group.

Along with the specific issues noted above, other general issues that may impact trial design and outcome involve patient-related factors. These elements include: temporal variability of symptoms and the impact of attention beliefs and expectancy, the use of patient-rated outcome measures, which is important in assessing patient population, and discrepancy in patients rated outcomes and clinician observed ratings, which may provide insights into the mechanisms underlying symptoms and treatment responses.

In summary, evidence-based medicine determination is established based on a research hypothesis, supportive evidence, and conclusions based on data that yield treatment recommendations. Ultimately, the desired outcome of the research agenda is the conduct of Class I studies (fully powered, masked outcome, randomized, controlled trials) leading to Level A recommendations (evidence for established care) for applied practice parameters⁴⁶ for evaluation and management of patients with FND.

Conclusion

Effective treatments for FND are available, however, one size does not fit all. Psychotherapy, rehabilitation-based approaches, and multidisciplinary treatment programs all have been shown to offer benefit for specific aspects of FND, but need to be studied further to replicate outcomes, aid in treatment stratification, and understand factors related to long-term treatment success. Additional

treatment modalities need to be explored and studied to better serve this diverse population, especially for patients refractory to current therapies. In terms of a research agenda, it is imperative that studies are conducted to address challenges in trial design and best practices for the implementation and dissemination of treatment programs. As new evidence-based treatments for FND emerge, dissemination of knowledge and improving access to care for this underserved patient population remain important areas to address.

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