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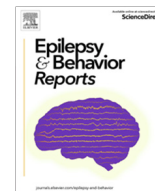
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The role of evidence-based guidelines in the diagnosis and treatment of functional neurological disorder

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ABSTRACT

Evidence-based clinical practice guidelines, based on systematic reviews of existing evidence, play an important role in improving and standardizing the quality of patient care in many medical and psychiatric disorders, and could play an important role in the diagnosis and treatment of functional seizures and other functional neurological disorder (FND) subtypes. There are several reasons to think that evidence-based guidelines might be especially beneficial for the management of FND. In particular, the interdisciplinary and multidisciplinary teamwork necessary for the care of people with FND, the current lack of formal clinical training in FND, and the rapidly expanding body of evidence relating to FND all make guidelines based on systematic literature reviews especially valuable. In this perspective piece, we review clinical practice guidelines, their advantages and limitations, the reasons why evidence-based guidelines might be especially beneficial in the diagnosis and treatment of FND, and the steps that must be taken to create such guidelines for FND. We propose that professional organizations such as the American Academy of Neurology and the American Psychiatric Association undertake guideline development, ideally to create a co-authored or jointly endorsed set of guidelines that can set standards for interdisciplinary care for neurologists and mental health clinicians alike.

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Introduction

Functional seizures and other functional neurological disorder (FND) subtypes are a common and highly disabling class of conditions. They are thought to be caused by a complex interplay of biopsychosocial vulnerabilities, often in the setting of psychosocial and/or physical triggers, and are frequently misdiagnosed as other neurological disorders [1]. FND is among the most common causes of neurological disability, diagnosed in approximately 16% of out-

patient neurology consultations, with functional seizures specifically diagnosed in approximately 25% of epilepsy monitoring unit admissions [2,3]. FND is associated with reduced quality of life, decreased employment, and increased dependence on public disability programs [4,5]. There is a growing body of evidence suggesting that FND may be associated with significantly elevated healthcare costs, morbidity and rates of mortality [5–8].

There is also growing evidence, including multiple randomized controlled trials, showing that FND can be effectively treated with psychotherapy and physiotherapy [9–13]. Single center randomized trials of physical therapy for functional movement disorder have found improved independence and mobility as assessed by

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the Functional Independence Measure, the Functional Mobility Scale, and by patient self-report [9,10]. For functional seizures, pilot randomized trials found that the frequency of functional seizures was reduced in participants randomized to receive cognitive behavioral therapy (CBT) or CBT-informed psychotherapy [11,12]. In addition, the first fully powered multi-center randomized controlled trial of CBT for the treatment of functional seizures was recently completed demonstrating significant benefits in secondary outcome measures of psychosocial functioning, psychological distress, somatic symptoms, and aspects of seizure control [14].

While guidelines based on expert consensus regarding the diagnosis and treatment of some FND subtypes currently exist, the growing literature of methodologically rigorous studies now makes possible the development of evidence-based guidelines for the management of FND [15–18]. Clinical practice guidelines are an important tool for standardizing and improving healthcare practice and offer a unique opportunity to improve diagnostic and treatment outcomes for patients with FND. In this perspective piece, we assembled an international, multi-disciplinary group of clinician researchers in FND to review clinical practice guidelines, guideline strengths and limitations, reasons why evidence-based guidelines might be especially beneficial in the diagnosis and treatment of FND, and steps that must be taken to create such guidelines for FND.

What are clinical practice guidelines?

Clinical Practice Guidelines are sets of systematically developed recommendations to standardize and improve healthcare practice in specific clinical circumstances [19]. Guidelines attempt to distill large bodies of information, and historically may draw on clinical experience, expert opinion, research evidence, or upon an amalgamation of these sources of information. Because of the risk of incomplete and biased data, guidelines based entirely on expert opinion or consensus or even on a narrative or non-systematic review of the literature are becoming less acceptable except in circumstances of limited research evidence [20,21].

Evidence-based guidelines increasingly draw on systematic reviews of research findings to support clinical recommendations [22]. Systematic reviews use clearly defined and reproducible literature search strategies to identify relevant evidence. Such reviews begin with a carefully defined clinical question, usually identifying a specific patient population, intervention, comparator (e.g., placebo, no treatment/test, or alternative treatment/test), and outcome measure(s) [23]. This clinical question then provides a framework for defining eligibility criteria for a comprehensive literature search, using a broad, clearly defined, and reproducible search strategy in specified databases, such as MEDLINE, Embase, the Cochrane Library, and EBSCO PsycInfo. Systematic reviews are ideally reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [24]. Evidence-based guidelines grade the amount and quality (or methodological rigor) of the available evidence before making recommendations. This helps guideline users to uniformly interpret the degree of certainty underlying specific recommendations. Grading of evidence is increasingly done using established rubrics, such as the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system, and the National Academy of Medicine's (formerly the Institute of Medicine's) overlapping criteria for trustworthy guidelines [21,25]. Judgements about the quality of evidence made using the GRADE system have good inter-rater reliability when compared with intuitive judgements [26]. While expert judgement may supplement research evidence, high quality evidence-based guidelines now explicitly and transparently iden-

tify exactly when and where such expert opinion plays a role in guideline development [23]. Ultimately, guidelines use the number and methodology classification (I-IV) of individual studies to determine an overall level of evidence for each conclusion, with evidence-based conclusions then serving as the basis for practice recommendations.

In the United States (US), large professional organizations such as the American Medical Association, the American Academy of Neurology, and the American Psychiatric Association are among the most prolific developers of clinical practice guidelines, along with government panels and cooperative groups. The National Guideline Clearing House, run by the US Agency for Healthcare Research and Quality, is a register of clinical practice guidelines that meet minimal quality criteria, though it is now threatened by lack of federal funding [27]. The primary audience for clinical practice guidelines are clinicians and patients making decisions about healthcare in specific clinical circumstances. Guidelines are also widely used by healthcare systems, policy makers, and insurers to measure quality of care, allocate healthcare resources, and determine insurance coverage. Guidelines also play an important role for healthcare systems as references for quality assurance and improvement efforts, and for researchers and funding organizations in identifying gaps in knowledge where future research is needed.

Advantages and limitations of evidence-based guidelines

There is a large and growing research literature showing that adherence to evidence-based guidelines lowers mortality rates and healthcare costs in disorders including breast cancer [28], ovarian cancer [29], pneumonia [30], heart failure [31], coronary artery disease [32], and atrial fibrillation [33]. Similarly, studies demonstrate that adherence to evidence-based guidelines results in greater symptom reduction in major depressive disorder [34], reduced medication adverse effects and greater symptom reduction in schizophrenia [35,36], lower healthcare costs in lower-back pain [37], and greater likelihood of achieving blood glucose control in diabetes [38]. In surveys, the majority of physicians endorse a need for evidence-based guidelines and believe that they improve patient care [39–41]. Indirect benefits of clinical practice guidelines are widely hypothesized but not yet formally studied [20,27,42]. These include directing healthcare resources toward evidence-based interventions and directing research attention and funding toward gaps in clinical knowledge.

On the other hand, historically, some physicians have raised concerns that guidelines might enforce overly rigid or “cookie-cutter” healthcare practices that fail to make allowances for individual needs, or that guidelines might increase legal liability for physicians who deviate from the guidelines or for professional organizations that publish or endorse guidelines. Surveys of physicians who have used clinical practice guidelines over the past 4 decades have not found these problems to be significantly borne out in practice [39–41]. However, some important limitations have become apparent with the ongoing development and use of guidelines.

Because guidelines require multidisciplinary groups of experts to collect and assess evidence and to generate recommendations, and because many clinical and research experts in the US collaborate with industry or for-profit healthcare corporations, there is a potential for real and perceived conflicts of interest [43]. This risk can be reduced through the implementation of the National Academy of Medicine's mandates for conflict of interest disclosure and voting and authorship restrictions among guideline developers [21]. Another limitation of guidelines is the proliferation of sometimes redundant guidelines, which can leave clinicians and

patients overwhelmed and confused. This issue can be mitigated through the use of a single publicly accessible and searchable central repository for evidence-based guidelines, such as the National Guidelines Clearinghouse. A third limitation is that guidelines rapidly become outdated as new evidence accumulates, with 1 in 5 recommendations becoming outdated within 3 years [44]. As a result, mechanisms (including the pre-requisite funding) for periodic updating of published guidelines are required. Finally, guidelines have only an indirect and delayed effect on clinical practice, and require large scale education, decision aids, and other implementation science interventions in order to achieve maximal impact [45]. Monitoring adherence to guidelines is essential to understand positive and negative clinical impacts of their use.

The potential role of clinical practice guidelines in functional neurological disorder

Abundant evidence exists showing that adherence to clinical practice guidelines improves patient care and outcomes in a broad range of medical, neurological, and psychiatric disorders. There is little reason to think that patients with FND could not also benefit from evidence-based guidelines, as the evidence-base in FND continues to grow. Moreover, there are several specific factors that might make guidelines particularly beneficial in the field of FND. These factors include the need for interdisciplinary and multidisciplinary teams in the evaluation and treatment of FND, clinicians' current lack of training in FND, and the relatively new and rapidly expanding research literature pertaining to FND.

FND, to an even greater extent than many other neuropsychiatric disorders, require a multidisciplinary team for effective diagnosis and treatment. Neurologists most often have the training and experience to diagnose (rule-in) FND and to differentiate them from other neurological disorders such as epilepsy, dystonia, and stroke with which FND are frequently misdiagnosed [1]. At the same time, mental health clinicians (psychiatrists, clinical psychologists/neuropsychologists, and psychotherapists), and rehabilitation specialists (physiatrists and physical, occupational, and speech therapists) most often have the requisite training and experience to provide evidence-based psychotherapeutic and rehabilitative treatment regimens [14]. Very few clinicians have the requisite training in both neurodiagnostics and psychotherapeutics to confidently and successfully diagnose *and* treat functional neurological disorders, in the absence of a multidisciplinary team.

As a result, clinicians involved in the evaluation and treatment of FND necessarily rely on clinical judgments, which they themselves may not have sufficient expertise to evaluate. For example, the majority of mental health specialists expressed doubt regarding diagnosis of functional seizures via video-electroencephalogram, when in fact this is the gold standard for the diagnosis of the disorder [15,46]. Similarly, many neurologists and emergency medicine clinicians are unfamiliar with the treatment of FND, and incorrectly regard patients with FND as "faking" their symptoms, rather than as experiencing a disabling disorder that is amenable to psychotherapeutic and rehabilitative treatment [47]. These clinicians often leave patients newly diagnosed with an FND with little guidance beyond the negative judgment that they do not have a neurological disorder such as epilepsy or a movement disorder, and a vague recommendation to seek evaluation from a mental health specialist. Guidelines – particularly guidelines endorsed by both neurological and psychiatric professional associations -- may therefore be helpful in establishing a shared understanding of FND across multiple clinical specialties as a serious and disabling neuropsychiatric disorder, in which best practices in diagnosis and treatment can bring real and meaningful improvements in patients' symptoms, function and quality of life.

Such shared understanding of best practices provides a foundation for necessary interdisciplinary collaboration, even among clinicians who do not have a pre-existing working relationship.

Beyond providing a necessary foundation for attitudinal changes and multidisciplinary collaboration among clinicians, evidence-based guidelines also can form a basis for supportive social changes, including reimbursement of clinicians and hospitals by public and private health insurance agencies, and social services support for patients and their caretakers. Reliable reimbursement of clinical care and social services support are necessary prerequisites to making treatment available and accessible to patients on a societal scale, beyond the efforts of specialty academic medical centers and research programs.

Another current challenge in the care of patients with functional seizures or other FND subtypes is the relative lack of formal clinical training relating to FND. The majority of mental health specialists report receiving little or no training in the management of FND [48]. Similarly, most neurologists and internists report important gaps in their training related to FND [49] (see also Milligan et al. Neurology Residents Education in Functional Seizures. Elsewhere in this issue). Evidence-based guidelines provide an objective framework around which to structure clinical education and facilitate curricular development. Evidence-based guidelines also provide the foundation for the development of standardized board examination questions and the educational milestones promulgated by the Accreditation Council for Graduate Medical Education (ACGME) [50]. Board examinations and ACGME milestones collectively set national standards for resident training in neurology, psychiatry, and other medical specialties.

Finally, the field of FND research is currently undergoing a period of exponential growth [1]. While this is bringing important advances in diagnosis and treatment, it also creates challenges for busy clinicians seeking to provide patients with guidance and recommendations, and for researchers seeking to build on prior studies. Evidence-based guidelines built on systematic reviews provide clinicians with unified and easily digestible summaries of the existing evidence and the resulting practice implications [20]. Similarly, systematic reviews and guidelines provide researchers and funders with clear maps of the existing literature, and of key lacunae as topics for future research.

Necessary steps to create evidence-based guidelines for functional neurological disorder

Clinical practice guidelines and reviews, based on expert consensus and narrative reviews of the literature, currently exist for the management of functional seizures and functional movement disorders – the most common forms of FND [15–18,51–53]. While these guidelines have raised awareness around FND, they have thus far failed to create a widely shared standard of clinical practice [47]. The few existing evidence-based guidelines have thus far been unable to muster sufficient evidence to support clinical recommendations [54]. Historically, professional organizations such as the American Academy of Neurology and the American Psychiatric Association have been reluctant to undertake the development of evidence-based guidelines because of the lack of fully powered randomized trials. This is because a minimum of at least one high quality randomized controlled trial is often (although not always) required to generate even the lowest level of evidence-based recommendations under the GRADE system and the grading variants used by professional organizations such as the American Academy of Neurology [23]. In the absence of such studies, evidence-based guidelines could be developed but would not support any evidence-based recommendations beyond recommendations for further study.

In June 2020, the CODES study group in the United Kingdom published their large multicenter trial of cognitive behavioral therapy for the treatment of functional seizures. Despite not showing a statistically significant beneficial effect of adding their model of cognitive behavioral therapy to standardized medical care in reducing seizure occurrence at 12 months post randomization, the study demonstrated effectiveness of the cognitive behavioral therapy intervention in improving length of time without seizures, aspects of quality of life, psychosocial functioning, psychological distress, and somatic symptoms [14]. Smaller randomized trials of other psychotherapies and observational treatment studies have shown reduction in seizures/movements, improvements in comorbidities, quality of life, and functioning, and in combination with the CODES trial results, the studies offer the possibility of the first evidence-based recommendations in the management of FND [11–13]. While the systematic collection and synthesis of evidence, the development of recommendations, and the authoring and approval of the written guidelines typically takes multiple years, this process can now begin. Because FND are managed by multidisciplinary teams, the guideline development process will ideally involve multiple professional organizations representing neurological, mental health, and rehabilitation clinicians either co-authoring or jointly endorsing a single set of recommendations. Such a guideline has been proposed within the American Academy of Neurology as an initial step.

Of note, existing randomized trials have focused on specific treatment modalities and specific subtypes of FND, such as CBT for functional seizures, or specialist physical therapy in an intensive outpatient (day program) setting [9,14]. Given the broad range of treatment modalities, symptom heterogeneity in FND, and the multiple etiological factors and mechanisms, additional randomized trials focusing on other treatment targets that combine expertise from different disciplines are needed to broaden the existing evidence base (see Fobian and Szaflarski. Identifying and evaluating novel treatment targets for the development of evidence-based interventions for functional neurological disorder. Elsewhere in this issue). In the short term, initial evidence-based clinical practice guidelines may be relatively narrowly tailored given the limited scope of existing studies. The development of useful clinical practice guidelines over the coming years, and the expansion of these guidelines as new studies are completed, will require the concerted efforts of an expert multidisciplinary task force.

Conclusions

Evidence-based guidelines provide important benefits in terms of improving and standardizing quality of care, and there are several reasons to think that they might provide particular benefit in improving the management of FND. In particular, the multidisciplinary teamwork necessary for the care of people with FND, the current lack of formal clinical training in FND, and the rapidly expanding body of evidence relating to FND all make guidelines based on systematic literature reviews especially valuable. Recently published randomized clinical trials make possible evidence-based recommendations for FND under formal systems for evaluating evidence such as the GRADE system and the National Academy of Medicine's criteria for trustworthy guidelines. Next steps will require professional organizations such as the American Academy of Neurology and the American Psychiatric Association to undertake guideline development, ideally to create a co-authored or jointly endorsed set of guidelines that can set standards for care for neurologists and mental health clinicians alike. Through collaboration with global organizations such as England and Wales' National Institute for Health and Care Excellence, the Scottish Intercollegiate Guidelines Network, and the international

Functional Neurological Disorder Society, we can begin to establish unified global standards for the management of FND.

Ethical statement

This opinion piece does not constitute human research and does not involve patients, research volunteers, or consent procedures.

Disclosures

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W. Curt LaFrance, Jr. has served on the editorial boards of *Epilepsia*, *Epilepsy & Behavior*; *Journal of Neurology, Neurosurgery and Psychiatry*, and *Journal of Neuropsychiatry and Clinical Neurosciences*; receives editor's royalties from the publication of Gates and Rowan's *Nonepileptic Seizures*, 3rd ed. (Cambridge University Press, 2010) and 4th ed. (2018); author's royalties for *Taking Control of Your Seizures: Workbook and Therapist Guide* (Oxford University Press, 2015); has received research support from the Department of Defense (DoD W81XWH-17-0169), NIH (NINDS 5K23NS45902 [PI]), Providence VAMC, Center for Neurorestoration and Neurotechnology, Rhode Island Hospital, the American Epilepsy Society (AES), the Epilepsy Foundation (EF), Brown University and the Siravo Foundation; serves on the Epilepsy Foundation New England Professional Advisory Board, the Functional Neurological Disorder Society Board of Directors, the American Neuropsychiatric Association Advisory Council; has received honoraria for the AES Annual Meeting; has served as a clinic development consultant at University of Colorado Denver, Cleveland Clinic, Spectrum Health, Emory University, Oregon Health Sciences University and Vanderbilt University; and has provided medico-legal expert testimony.

Steve Martino reports no competing interests.

David L. Perez has received honoraria for continuing medical education lectures on functional neurological disorder and is on the editorial board of *Epilepsy & Behavior*.

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Jon Stone receives royalties from UpToDate for articles on FND and has received honoraria for continuing medical education lectures on FND. He runs a free self-help website for people with FND at neurosymptoms.org. JS carries out independent expert medicolegal work including in relation to FND. JS is secretary of the FND society and on the medical advisory board for FND Hope and FND Action. He has received funding from Scottish Government and the National Institute of Health Research.

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