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Nonepileptic seizures treatment workshop summary★

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Abstract

In May 2005, an international, interdisciplinary group of researchers gathered in Bethesda, MD, USA, for a workshop to discuss the development of treatments for patients with nonepileptic seizures (NES). Specific subgroup topics that were covered included: pediatric NES; presenting the diagnosis of NES, outcome measures for NES trials; classification of NES subtypes; and pharmacological treatment approaches and psychotherapies. The intent was to develop specific research strategies that can be expanded to involve a large segment of the epilepsy and psychiatric treatment communities. Various projects have resulted from the workshop, including the initial development of a prospective randomized clinical trial for NES.

Keywords

Nonepileptic seizures; Somatoform disorders; Conversion disorder; Treatment; Clinical trials; Pharmacotherapy; Psychotherapy

1. Introduction

Psychological nonepileptic seizures (NES) are neuropsychiatric disorders that present with a combination of neurological signs and underlying psychological conflicts and without associated epileptogenic pathology. For more than a century, the medical community has accumulated a substantial amount of data on and insights into the phenomenology, epidemiology, risks, comorbidities, and prognosis of NES. The use of intensive video/electroencephalography (video/EEG) monitoring has also increased our knowledge of NES. For example, we know that NES are often unresponsive to conventional treatments and can have devastating health and social consequences. The causes of NES are thought to be multifactorial, and result from a combination of developmental and environmental insults, though no specific pathophysiological (e.g., animal) model exists. Currently, progress is being made toward understanding the comorbid psychiatric diagnoses and

★This paper is dedicated to the memory of Dr. John Gates, who was instrumental in the first two NES workshops, and who has contributed greatly to our understanding of NES in the past two decades.

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neuropsychological characteristics of patients with NES. However, the lack of biological models, clear diagnostic classifications, and rigorously validated interventions continues to have a negative impact on treatment development. Thus, there is a great need for interdisciplinary collaboration to address the issue of approach to treatment.

Conceptually, as the disciplines of neurology and psychiatry are being reunified, a joint perspective of mind/brain interactions is regaining prominence. The “Decade of the Brain” brought great therapeutic advances for many neuropsychiatric disorders. However, NES still occupy the gap between neurology and psychiatry, and treatment remains poorly studied. Despite our knowledge, we have not progressed much beyond anecdotal reports of treatments for NES, and no blinded, randomized, controlled trials of treatment for the disorder have been completed. The purpose of the NES Treatment Workshop was to stimulate future research in this understudied area.

The workshop, which took place in Bethesda on May 1–3, 2005, was sponsored by the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute of Mental Health (NIMH), and the American Epilepsy Society (AES). Participants included a multidisciplinary group of neurologists, psychiatrists, neuropsychiatrists, psychologists, neuropsychologists, statisticians, nurses, and other health researchers familiar with NES, whose focus was to propose a research agenda for NES treatment trials. This effort built on the two NES conferences organized by Dr. John Gates and the NINDS in the 1990s, held in Fort Lauderdale and Bethesda. Results of these workshops yielded information on diagnosis, neurological and psychiatric comorbidities, and psychological functioning in patients with NES, which was subsequently published in a book now in its second edition [1]. The goal of the current workshop was to lay the groundwork for optimizing NES treatment strategies and clinical trial designs.

Goals of the workshop included:

- characterization of diagnostic and treatment models of NES;
- assessment of the potential efficacy of therapies in individual patients by examining past treatment reports and pilot trials for NES;
- establishment of a collaborative network that enables investigators to design and implement controlled treatment trials for NES.

As a means of focusing discussion, the meeting began with a brief presentation by the organizers as to workshop objectives:

- A history of “psychogenic” diagnoses
- A brief overview of diagnostic classification in NES
- A review of treatment studies in NES: progress and obstacles
- An overview of pharmacology and psychotherapy in NES in adults and children: strategies for treatment development
- A review of clinical trials in behavioral disorders relevant to NES

These introductory lectures provided a framework for the discussion groups that followed. Each group was asked to use three questions to guide their discussions: (1) What do we know about existing treatments for NES? (2) What do we need to know about NES to develop better treatments? (3) How do we achieve the goal of effective, scientifically validated treatments for NES?

2. NES treatment workshop group task

The goal of the workshop as a whole was to review issues and generate testable research hypotheses. Prior to the meeting, participants were organized into five subgroups:

Pediatric Subgroup

Presenting the Diagnosis of NES Subgroup

Classification Subgroup

Outcome Measurement Subgroup

NES Treatment Trial Subgroup

Each subgroup was charged with identifying the major problems and questions most relevant to NES treatment in its topic area, and recommending strategies for addressing the areas. The major issues and recommendations from each subgroup are now summarized.

3. Pediatric NES subgroup summary

3.1. Background

A pediatric subgroup was included because of developmental changes in NES characteristics, and because even less information is available about the disorder in children.

From the developmental perspective, there are differences in the incidence, etiology, clinical presentation, treatment, and outcome of NES in younger compared with older patients [1]. Thus, children who experience nonepileptic events have a wide range of seizurelike manifestations [1–4] that vary by age [1]. In children younger than 5, these include physiological nonepileptic events, including stereotyped movements, hypnic jerks, parasomnias, and Sandifer syndrome [1–4], as opposed to psychological NES, which are noted to occur after age 6. In children aged 5–12, NES might be an expression of a psychogenic conversion disorder, inattention or daydreaming, stereotyped movements, hypnic jerks, and paroxysmal movement disorders. However, in adolescents, conversion disorder is the main diagnosis underlying NES [1]. In addition, comorbid epilepsy is more commonly reported in younger children with NES than in older children or adults with NES. Forty-eight percent of children with NES under the age of 5 have comorbid epilepsy, whereas only 25% of those aged 5–12 years and 19% of adolescents do so [1]. It was noted that in children of all ages, the manifestations of syncope also can be confused with both epilepsy and NES [5].

Unlike adult NES, there is a dearth of information regarding the incidence, etiology, clinical presentation, cognitive, linguistic, and social skills, treatment, and outcome of NES in

children and adolescents. For example, the gender distribution of NES appears to change during development, being similar in young boys and girls, but higher in female teens than male teens [1]. These findings are based on a small sample size and need to be replicated. Similarly, other than a number of small studies of seizure outcomes in children and adolescents with NES [6–9], there have been no controlled studies of comorbid epilepsy or of the behavioral and functional outcomes of youths with NES.

3.2. What needs to be assessed?

To address this question, the subgroup began by discussing the available data:

Eleven to fifteen percent of children in telemetry units have NES [1,4]. There are no differences by age in the presentation of motor versus nonmotor “unresponsive” NES [1].

Forty-four percent of 16 cases had a past history of head trauma in the single study that examined premorbid neurological risk factors [4]. Nine- to eighteen-year-olds with psychogenic NES ($N=34$) had the following comorbid psychiatric diagnoses: mood disorders (major depression, bipolar disorder, dysthymic disorder) in 11 (32%); separation anxiety in 8 (24%); posttraumatic stress disorder (PTSD) in 3 (10%); other anxiety or behavioral disorders in 3 (10%); and brief reactive psychosis in 2 (6%) [9].

With respect to prior traumatic events, 11 (32%) had a history of sexual abuse (particularly those with mood disorders); 2 (6%) had a history of physical abuse; and 15 (44%) had severe family stressors (such as recent parental divorce, parental discord, or death of a close family member) [9].

A greater than 70% improvement 1.5 to 4 years after the initial diagnosis was reported in children and adolescents [7–9]. Seizure-free percentages were approximately 75% or better for children compared with 25–40% for adults at 1, 2, and 3 years of follow-up [10].

Predictors of good outcome included multiple seizure types, younger age at presentation, and female gender. Comorbid epilepsy predicted a worse outcome [7].

Other relevant data included the following:

Children with other types of somatic disorders (e.g., conversion disorder, chronic pain, body dysmorphic disorder) had high rates of academic and social difficulties, as well as difficulties identifying and/or expressing emotions (alexithymia) (see review in [11]).

Correlates of functional symptoms identified predominately in pediatric pain patients include: female gender (after puberty); substance use; comorbid anxiety disorders; prior medical illness, physical injury, and hospitalization; childhood trauma; school problems; and parent factors (i.e., a distressed parent, a parent with physical or psychiatric symptoms, parent discouragement of

children's positive coping efforts, or excessive parental attention to symptoms) [9,12–20]. Similar studies have not been conducted in children with NES.

These findings illustrate the differences in psychiatric comorbidities between children and adults with NES, with lower rates of PTSD and depression in children, and the better prognosis for NES resolution in children.

3.3. Recommendations

The Pediatric Subgroup concluded that more information was needed on NES in terms of: demographics, seizure semiology, seizure control, type of antiepileptic drugs (AEDs), neurological risk factors, family functioning, comorbid psychiatric diagnoses, and psychosocial risk factors (i.e., trauma, loss, conflict, and impaired academic and social functioning).

Because of the morbidity, marked cost of health care services, and poor psychological outcome in children with late or no intervention, the Pediatric Subgroup discussed the importance of early identification and intervention, particularly for those with conversion and other comorbid psychiatric disorders, using an integrated biological, psychological, familial, and social approach.

Finally, in addition to identifying children and adolescents at risk for development of NES, the subgroup thought that it was important to develop treatment studies for these patients. However, a decision was made to focus first on obtaining basic descriptive data before embarking on treatment studies. Knowledge about the rates of conversion disorder, mood disorders, anxiety disorders, psychosis, as well as attention deficit hyperactivity disorder (ADHD) and other disruptive disorders would help determine if cognitive behavioral therapy, psychotropic drugs, or a combination of both approaches is indicated.

To summarize, the information currently available on NES in children and adolescents is based on a few descriptive studies, some of which have been small, retrospective, and have focused on NES rather than on behavioral and functional outcome. The pediatric NES subgroup concluded, therefore, that the gaps in our knowledge of the biopsychosocial features of children with NES need to be addressed first, through well-designed and hypothesis-driven prospective studies that include established and standardized measures. The findings of such studies will provide the basis for pediatric intervention studies.

4. Presenting the NES Diagnosis Subgroup summary

A major obstacle to treatment of NES is patients' refusal to accept the diagnosis. The reasons for refusal vary and include the concern that they will be thought of as being "crazy" or that they are "faking their spells." The way in which the diagnosis of NES is presented to patients and their families following video/EEG monitoring is therefore considered pivotal in acceptance of the diagnosis and of the recommendation to pursue further psychological or psychiatric treatment.

To minimize rejection of the diagnosis of NES, various authors have suggested protocols on how to inform patients of this diagnosis [21]. The complexity of the problem became

apparent in the extensive subgroup discussions that followed the initial brief review. In short, there was a lack of consensus on the terminology to use when referring to NES, whether a psychogenic causality could be implied when no axis I or II diagnosis is present in the small subset of NES patients, and if a psychiatrist/psychologist should be present during discussion of the diagnosis. To resolve this disagreement, the subgroup recommended two observational multicenter studies.

The first should identify which approach is most effective: (1) calling the event functional versus psychogenic versus another term; (2) identifying it as a nonepileptic seizure (NES) versus a nonepileptic event (NEE); (3) using the patient's videotaped event versus a standardized verbal explanation; or (4) providing the patient with written educational material versus a clinician's verbal explanation. The primary outcome variables would be acceptance of the diagnosis of NES and acceptance of recommendations for further psychiatric/psychological treatment.

Additional variables could include level of education, IQ, age, gender, ethnicity, mood at the time of diagnostic video/EEG monitoring, and history of prior video/EEG diagnostic evaluation, information on NES, or psychiatric treatment.

The second study should identify interrater reliability on the diagnosis of NES. This was envisioned to be a multicenter study in which investigators who were blind to the diagnosis would rate video clips of NES, epileptic seizures mimicking NES, and physiologic NEE (including examples of sleep disorders, movement disorders, syncope, and panic attacks). Interrater agreement would then be measured with a κ statistic.

5. Classification Subgroup Summary

The focus of the Classification Subgroup was to review issues relevant to NES classification. The goal of classification is to identify independent variables that are predictive of treatment efficacy.

5.1. General issues regarding classification and subtyping

5.1.1. Limitations of present standard definitions of psychiatric disorders in neurological populations—The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Revised (DSM-IV-TR) [22] is not popular among many neurologists, who find that it fails to capture distinctive features of psychiatric presentations in epilepsy and other neuropsychiatric conditions. The absence of classifying personality alterations in epilepsy is probably the diagnostic issue most commonly invoked as illustrating DSM-IV-TR's deficiency in this regard. There currently is no consensus on an alternative classification system. Even if one existed it would be difficult for it to gain widespread use because the psychiatric community and health care insurers universally use DSM-IV-TR. It would be a monumental effort to create a widely adopted alternative to DSM-IV-TR, and for practical purposes, it appears necessary to work within the DSM-IV-TR diagnostic framework.

Some of the problems with DSM-IV-TR would be common to alternative classifications. This is largely because the biological bases of most psychiatric disorders are not understood, which limits the use of pathophysiology as a validating principle (not excluding our growing knowledge of dopamine hypersensitivity in schizophrenia, serotonin deficiency in depression, autonomic hyperarousal in anxiety disorders, etc.). Another problem is the “lumper versus splitter” dilemma. “Lumpers” tend toward broadly inclusive categories that might obscure important differences within a population. “Splitters” tend toward classification on the basis of fine differences that might create an unwieldy excess of trivial diagnostic categories.

5.1.2. Dissociative versus somatoform disorder—This is an old and fundamental debate regarding the nosological position of conversion, the most common NES presentation, within psychiatric disorders. DSM-IV-TR subsumes Conversion Disorder under Somatoform Disorders, whereas the International Statistical Classification of Diseases and Health Related Problems (ICD-10) [23] regards conversion as a Dissociative Disorder. In DSM-IV-TR, the reason for classification of Conversion Disorder within Somatoform Disorders is “to emphasize the importance of considering neurological or other general medical conditions in the differential diagnosis” [22].

Both systems agree that dissociation is a very important mechanism in the production of conversion symptoms, and the DSM-IV-TR acknowledges that the Dissociative and Conversion categories share common features: “Both disorders involve symptoms that suggest neurological dysfunction and may also have shared antecedents.” DSM-IV-TR specifies that “when both conversion and dissociative symptoms occur in the same individual both diagnoses should be made.” However, DSM-IV-TR confines the Dissociative Disorder classification to relatively extreme presentations such as Dissociative Identity Disorder and Dissociative Fugue. This avoids the situation that Conversion Disorder would nearly always be classified as both a Somatoform Disorder *and* a Dissociative Disorder.

5.2. Specific research questions regarding classification and subtyping

Should “reinforced behavior” be designated as a distinct subtype of NES? The term is intended to designate NES, usually in the context of developmental disorders or mental retardation, for which a behavior modification approach (and not a cognitive or psychodynamic approach) may be indicated [24]. Given that most NES, including those in developmentally normal individuals, are “reinforced” in some sense, how do we define the diagnostic boundaries of such behavior?

With respect to the DSM-IV-TR criteria for conversion disorder, is the “B” criterion useful and valid (p. 457: “Psychological factors are judged to be associated with the symptom...”) ? Criticisms of this criterion include its quality of post hoc reasoning and lack of specificity in that physiological epileptic seizures are frequently associated with, if not exacerbated by, psychological stress.

How is the DSM-IV-TR “C” criterion assessed (“The symptom or deficit is not intentionally produced or feigned...”) ? Regardless of whether one believes that a dynamic explanation exists for the intent, its unconscious nature appears essential to the diagnostic concept of

conversion. However, there is substantial uncertainty regarding the accuracy of our attribution of conscious versus unconscious intent or, indeed, whether “conscious” and “unconscious” are nonoverlapping states. Likewise, the issue of how to clinically distinguish intentionality in patients is relevant for cases of malingering. Can this uncertainty be avoided when diagnosing conversion?

What is “dissociation”? In DSM-IV-TR, *dissociation* is defined as a “failure in the usually integrative functions of identity, memory, or consciousness” [22]. Should it be regarded as a unitary concept? If not, what are its underlying constituent dimensions?

5.3. Variables and issues relevant to treatment decisions

Putative subtypes of dissociation (detachment vs compartmentalization) [25]

Presence versus absence of abuse or trauma history

Presence of genetic markers associated with antidepressant response, regardless of phenotypic expression of clinical depression [26]

Conversion versus nonconversion NES [27,28]

Utility of functional neuroimaging in subtyping NES (e.g., dissociation versus conversion versus reinforced) [29].

Presence or absence of neurological impairment (e.g., EEG abnormality, history of traumatic brain injury, “soft signs,” or nonverbal learning disability)

A specific role for right hemisphere dysfunction [30]

Presence or absence of comorbid psychopathology

Status of family or relational systems that may reinforce illness behavior

6. Outcome Measurement Subgroup summary

The Outcome Measurement Subgroup addressed questions that would help inform development of NES treatment studies. One major purpose of outcome measurement in NES is to operationalize the dependent variables for hypotheses regarding treatment outcome.

6.1. General issues regarding outcome measurement in NES

6.1.1. Should choice of outcome measures be linked to an underlying theoretical model?—Several conference participants emphasized that outcome measures should be linked to an explicitly stated theoretical model of underlying etiology or the mechanism of the intervention. It was pointed out that if the intervention improved seizure control without changing the hypothesized etiology, the validity of the treatment could be called into question. On the other hand, it was suggested that more pragmatic endpoints such as driving, work, social restrictions, and patients’ perception of distress would be valid outcome variables, and may be more useful for practical-based outcome studies. The question of whether patients would care about changes in “illness perception” if their seizures were not controlled was raised. This issue suggests that patient-oriented outcome measure development may be warranted, for use with the standardized tools already

available. The use of similar adjunctive measurement tools has been advocated for epilepsy treatment outcome studies previously [31].

The attendees agreed that there is no single etiology for NES (see Classification Subgroup Summary), although several leading causal contenders were nominated. Endogenous anxiety, avoidance behavior, dissociation, nondissociative posttraumatic stress, abuse, interpersonal dynamics, personality structure, and societal factors may all play a predisposing, precipitating, or perpetuating role and may interact with each other. Several theoretical models were described to account for NES development, including psychodynamic, cognitive-behavioral, and learning theory [32–34]. For example, in a recent study, Goldstein et al. [34] explicitly tested a “fear avoidance” model of NES using cognitive-behavioral therapeutic techniques. This prospective, nonrandomized trial used specific instruments tapping the proposed theoretical constructs under investigation.

6.1.2. Statistical power and breadth of focus in outcome measures—Selecting a single primary outcome variable or a few key variables helps minimize the statistical burden placed on the study design in terms of reducing the proliferation of false-positive errors. The more outcome measures employed, the more demand is placed on establishing statistical power of the intended clinical trial (i.e., increased sample size, increased effect size of measure). A battery assessment with focus and breadth may help strike a balance between too narrow or too broad an outcome focus. A narrow outcome focus may miss important changes that an intervention may produce. A broader outcome approach may be sufficiently comprehensive to test key areas of a theoretical model that underpins the intervention trial. From a statistical point of view, allowing for a greater breadth of measurement may reveal significant treatment effects that would not be revealed with narrowly focused outcome measures.

In view of the etiological complexity of different NES disorders, outcome measures focusing on one particular factor (like fear avoidance) may not apply in a substantial proportion of cases. If an outcome measure that reflects a relatively narrow etiological model is chosen, it may show no effect across a treated group, although it may well have been relevant for some of the people treated. The use of measurements that have good specificity for their targets will help in maintaining the clarity of research conclusions regarding etiology and intervention.

6.1.3. What variables or domains should be regarded as reflecting “outcome”?—Subgroup members and other conference attendees offered a diversity of potential measures. As previously mentioned, several workshop attendees emphasized that each measure be linked in some fashion to the underlying etiological model proposed to account for NES behavior. It was pointed out that the selection of outcome measures would necessarily depend on the intervention model designed. Overall, several areas of NES-relevant outcome measures were identified as potentially useful markers of intervention endpoints. Identified areas included psychosocial outcomes (e.g., employment status, return to prior functional status, family functioning), clinical outcome (e.g., seizure outcome, seizure pattern), psychiatric status and symptom presentation (e.g., depression, avoidance behavior, other dissociative symptoms), health-related quality of life, medical resource

utilization (e.g., emergency department visits, hospitalization, medication usage), and psychophysiological markers (e.g., arousal).

The subgroup concluded that a standard efficacy approach (seizure freedom or reduction) that was supplemented by carefully selected generic patient-oriented quality-of-life and health-care utilization measures would probably be most easily interpreted by the medical community. However, several conference participants noted that having a range of outcome measures would be valuable in any intervention trial design. For example, the Goldstein et al. trial employed measures assessing clinical outcome (seizure frequency diary), psychosocial outcome (work and social adjustment), psychopathology outcome (fear, depression), as well as several secondary outcome measures of health perceptions and locus of control [34]. Reuber et al. [35] examined long-term NES outcomes from the standpoint of seizure outcome and government disability status and found that several clinical and psychological factors were associated with better prognosis. However, they pointed out that some variables are not conducive to intervention, such as history of better education and less violent seizures. Similarly, changing maladaptive personality characteristics may also prove difficult. Targeting personality characteristic change may also prove difficult, but they suggested that it may be possible to “concentrate on the identification and management of stressors or triggers in the (social) environment that interact with personality vulnerability” [35].

6.2. Specific issues regarding outcome measurement in NES

6.2.1. How can socioeconomic/medical utilization outcomes be measured?—

Some participants advocated socioeconomic/medical utilization outcomes, at least as secondary outcomes. It was felt that an intervention with positive impact on these more society-level outcomes would have the additional advantage of support from current cost-effectiveness models. If an intervention resulted in a reduction of medical resource utilization or return to employment, then a stronger case could be made for acceptance of that intervention as a standard of care [36,37]. The Martin et al. [37] study demonstrated that utilization rates (emergency department visits, medication usage, diagnostic procedures) could be measured and that changes do occur in the pattern and use of medical services after definitive diagnosis. Demonstrating that health care expenditures are reduced by NES diagnosis and intervention would be important and compelling data for insurance carriers. The psychiatric intervention literature examining cost-effectiveness of various pharmacotherapies and psychotherapies has shown this to be a successful strategy for encouraging widespread acceptance of a given intervention (e.g., Schoenbaum et al. [38]).

6.2.2. How do the qualitative and quantitative features of nonepileptic events reflect outcome?—

There was some debate regarding the relevance of including change in seizure characteristics (frequency, presentation, etc.) as outcome variables. Some participants felt that assessing change in seizure frequency during an intervention might reflect change in the underlying etiological process. It was pointed out that the patient's focus might change during the intervention, as the initial preoccupation with symptoms and seizure frequency (i.e., “harm to self”) shifts to an awareness of deeper psychological issues, and that this might be reflected in a change in seizure frequency. As is the case with

epilepsy, improvement or positive change in quality of life for patients with NES is often negligible unless seizures totally abate [39]. Others felt that seizure frequency should be considered a secondary measure, with change in other pertinent psychological variables identified as the primary targets. Certainly, support was expressed for the inclusion of seizure frequency with the other outcome variables. This raised further discussion as to the reliability of seizure frequency measurement. This topic has been thoroughly discussed in the epilepsy treatment literature (e.g., Baker et al. [40]), but not in terms of NES. It was agreed that a spectrum of seizure measurement should be included that would capture aspects of the seizure behavior. This could include seizure frequency, seizure severity, seizure triggers, and seizure semiology.

6.2.3. Potential dependent variables/outcome domains

Seizure frequency

Individual concerns (e.g., Epilepsy Foundation of America Concerns Index)

Employment (return to work), disability status

Psychiatric symptoms (DSM-IV-TR axes I and II, Beck Depression Inventory, Hamilton, Symptoms Check List-90, etc.)

Personality characteristics

Health-related quality of life

Psychophysiological variables (e.g., arousal)

Family/psychosocial factors (e.g., Family Assessment Device)

Medical resource utilization (e.g., emergency department visits, hospitalizations)

Illness cognition/perceptions (e.g., label, cause, treat-ability, time line, consequences)

It should be noted that the assessments/tools in the preceding list include measures of how people feel in general and about their seizures, but not what they think about them. There is evidence from health psychology studies in other areas that illness cognitions or perceptions are related to outcome.

6.3. What are the preferred characteristics of a given outcome measure for NES clinical intervention trials?

As mentioned before, the outcome measures should include items linked to the theoretical constructs of underlying psychopathology that are being investigated.

The measures chosen should be instruments/techniques that have demonstrated the most robust psychometric properties (i.e., reliable, valid) and the most data supporting their use. Excellent reviews of this topic have been presented and have described ideal measurement features such as the responsiveness of the instrument to change from the intervention [41,42].

The literature should be searched for available measures already in existence that could be applied to the intervention study. However, new instruments to assess NES treatment outcome could be constructed. Instrument development under the umbrella of a NES treatment trial task force could elicit expertise from multiple sources.

Instruments should be of a length that patients can readily complete in a timely manner. Patient burden may be considerable with a lengthy, repetitive questionnaire packet. In such cases, participants are less likely to complete their responses, increasing the probability of missing or inaccurate data.

In addition to the number of instruments used, the level of complexity of the instruments should be taken into consideration. That is, will patients understand what they are completing? Evidence suggests that neurocognitive impairments can be observed in the NES population [43] and this may hinder accurate comprehension of the intended questionnaires that are used for outcome assessment.

Measurement tools should be sensitive to change at multiple time points while the intervention is in progress. For example, using change in medical disability as an outcome may not be a sensitive endpoint after 6 months. However, assessing change in mood status or seizure frequency at the same 6-month endpoint may be more likely to reveal an effect. Outcome measures that may be more sensitive to postintervention short-term change (i.e., weeks/months) may include (but are not limited to) seizure frequency, mood status, medical resource utilization, anxiety symptoms, self-report of somatic complaints, and reduced avoidance behaviors. Other outcome measures that may not be sensitive to change until a longer postintervention interval has elapsed include change in vocational status, medical disability status, or dynamic relationships between patient and therapist [44].

Issues pertaining to the importance of querying multiple sources of information were discussed by the NES workshop participants. Reliance on self-report data may limit an outcome measure's validity. Intervention trials should use instruments that gain clinical data from a range of sources, including the patient, his or her family members, or the treating physician. Clinician rating forms are commonly employed in clinical trial design to assess a variety of outcomes including mental status and mood. Family reporting of participant mood, behavior, or other clinical variables (i.e., seizures, medical resource utilization) may also be helpful in gathering a reliable estimate of the outcome variable of interest.

6.3.1. Proposed characteristics for NES clinical trial outcome measures—The outcomes should:

- Be linked to theoretical constructs of underlying psychopathology
- Employ standardized measures with solid psychometric properties
- Use existing measures available in the scientific literature from other areas
- Employ measures that are sensitive to the intended treatment changes: short-term change (weeks/months), long-term change (years)

Use measures that the subjects can complete and comprehend Limit the burden of the outcome battery (time and psychological)

Use a multi-informant approach to outcome measurement (self-report, clinician rating scales, observational, neuropsychological, generic quality-of-life measures allowing for across condition comparison)

Given that there is not only cross-sectional but also longitudinal heterogeneity in patients with NES, the subgroup noted that for a treatment study in this area, interventions can either be quite basic and widely applicable to a less selected or restricted NES patient population or can be more specific in its criteria (for newly developed NES, for NES in the context of trauma or somatization disorder, for those with mixed NES/epilepsy or those with lone NES, etc.).

6.3.2. Suggested inclusion/exclusion criteria for a treatment study on NES

6.3.2.1. Inclusion criteria

Video/EEG confirmation of NES, capturing a typical event

Diagnosis by DSM-IV-TR criteria of Conversion Disorder presenting as NES, or Undifferentiated Somatoform

Disorder or Somatization Disorder in which NES occurs as a conversion symptom

6.3.2.2. Exclusion criteria

Malingering

Pending litigation

Major psychotic disorder; i.e., schizophrenia, schizoaffective disorder

Acute need for psychiatric hospitalization

Pregnancy

Nonconversion NES [27]

IQ < 70

Neurological disorder associated with progression; i.e., multiple sclerosis, malignant neoplasm (The presence of epilepsy should be duly noted, but epilepsy is not exclusionary.)

7. NES Treatment Trial Subgroup summary

The NES Treatment Subgroup attempted to review the present status of intervention strategies. A vast array of interventions have been suggested to be of some use in treating patients with NES, but we found no double-blinded, randomized, placebo-controlled trials in two extensive literature reviews [45,46]. In developing a multicenter study, the subgroup realized the potential statistical complexity of evaluating too many interventions and recognized the advantage of “keeping it simple.” Dr. Goldstein and Dr. Mellers (who are

evaluating a cognitive-behavioral intervention at the Maudsley Hospital in the United Kingdom) and Dr. LaFrance (who is investigating a pharmacological intervention in the United States) will have data on their respective pilot randomized, controlled studies by early 2007, which will inform the multicenter trial protocol. The subgroup advocated “lumping instead of splitting” with respect to NES diagnostic inclusion (as noted in the Classification Subgroup and Outcome Subgroup summaries) and discussed the following treatment protocol proposal.

The recommended NES treatment study would have three arms: a neurological follow-up control group, a cognitive-behavioral therapy (CBT) intervention group, and a psychopharmacological treatment group. Patients would be randomized into one of these groups. Exclusion criteria would include current suicidality, current alcohol and illicit substance abuse, current psychosis, as well as the presence of pending litigation and the other exclusions presented earlier. Only patients with current NES without concurrent epilepsy would be included in this initial study, but a history of epilepsy would not be exclusionary. In disagreement with the Outcome Subgroup, the NES Treatment Trial Subgroup recommended that patients with current, concomitant epilepsy be excluded, at this stage. Bipolar disorder would not be a reason for exclusion, but there was debate on this issue with the differences over the antiepileptic drug issue (discussed later).

A neurological and psychiatric evaluation would be completed in all patients. The primary outcome would be NES prospectively collected seizure logs. The pros and cons of using seizure count as the primary outcome were discussed. In addition to the dependent variables outlined in the previous section, other scales considered for secondary analysis might include: Beck Depression Inventory, Dissociative Experiences Scale, SCID and SID-P, Symptoms Check List—90, Quality of Life in Epilepsy—31, a trauma questionnaire, a coping scale, a family functioning scale, and a general function scale. In addition, the Hypnotic Induction Profile and the Barrett Impulsivity Scale could also have some utility, but administration and training may be an issue with the Hypnotic Induction Profile.

Addition or deletion of medications induced a lively discussion. Based on the methodological idea of simplicity in interventions, one proposal was that all medications would be fixed on the dosages at the time of trial evaluation. The only intervention would be the addition of an SSRI, or addition of CBT to the current regimen, or neurological follow-up in the treatment-as-usual control group. Reasons were given for not withdrawing AEDs: First, AEDs are used in patients with NES for their effects on mood and impulsivity and for headache or pain prophylaxis. Second, withdrawing a drug is an intervention in itself. Finally, after diagnosis with video/EEG or long-term monitoring, patients are often returned to a previous drug regimen before discharge. Many patients with NES would have been treated with AEDs for a number of years prior to enrolling in the trial, and withdrawing a medication would be a significant intervention. After the trial was concluded, the effect of withdrawal of AEDs could be evaluated in a secondary analysis.

Conversely, the argument against continuing a patient on AEDs was as follows: First, if the diagnosis of current epilepsy is excluded in *all* patients, there is no indication for continuing AEDs for NES treatment. Patients have demonstrated safe withdrawal of AEDs when the

diagnosis of NES has been documented by video/EEG monitoring [47]. Most importantly, to continue AEDs incurs the risks of toxicity, teratogenicity, and expense. Second, although withdrawal of AEDs is a treatment in itself, this would be carried out equally in all three treatment groups and so would not bias outcome. Finally, from a CBT perspective, continuing AED therapy in lone NES would reinforce the patient's belief that he or she still has epileptic seizures and would mitigate against the acceptance of psychological factors in the production of seizure activity. In addition, anxiety about stopping the AED could be dealt with during the treatment sessions, and similar reassurance about AED discontinuation could be given to the control group. This antianxiety intervention could be evaluated in economic terms and would also be an important outcome measure.

The argument against continuing AEDs in patients with NES who have unipolar depression was discussed. While many patients have a mood disorder, other treatments (SSRI, psychological therapies) would be first-line interventions, not the mood stabilizers. Also, mood-stabilizing efficacy has not been established for many commonly used AEDs (e.g., phenytoin, levetiracetam, topiramate). Where it is better established (carbamazepine, valproate, and lamotrigine), the evidence is in patients with bipolar affective disorder, not mild depression or dysthymia, as is more common in patients with NES. In addition, AEDs may have negative psychotropic properties and discontinuation would have a positive effect. To fix AED dosage on enrollment, we would have to make clear to patients that they would be asked to remain on AEDs for the duration of the study, even though this medication was no longer indicated in their case and could be associated with a range of adverse effects. If AEDs were tapered, an allowance could be made for those patients who meet criteria for bipolar affective disorder, as measured by the SCID, where AEDs with confirmed psychotropic effects in the disorder, i.e., valproate, carbamazepine, and lamotrigine, would be continued. In conclusion, there are pros and cons to continuing or to discontinuing AEDs in the proposed trial, and this is an ongoing discussion.

A baseline observation period would establish if NES persisted with enrollment. During a 1-month waiting period, we would investigate the concept that patients may improve just from having been given a definite diagnosis and being reassured that they do not have epilepsy.

After 1 month, if NES persisted, patients would be randomized to one of three groups. The first group would be seen by their neurologist on a twice-a-month schedule, and AEDs would remain stable (or would be withdrawn, as discussed earlier). The evaluating neurologist would also see the other members of the study with the same frequency. The second group would receive CBT intervention for approximately 12 sessions over a 4-month period, and this would be based on the Maudsley protocol. The pharmacological intervention would follow that of Dr. LaFrance's trial, i.e., sertraline treatment under the same inclusion criteria implemented in his current pilot randomized control trial. Finally, we discussed the possibility of patients crossing over into the CBT or pharmacological arm after the 4-month intervention was completed. Another possibility is tailored intervention, perhaps based on specific diagnostic comorbidities in NES (see Rusch [44]).

The statistical feasibility of this three-armed, randomized controlled trial was discussed, including the lack of effect sizes established in NES treatment trials, the randomization

procedure with or without stratification of risk factors, and potential site intervention differences. The proposed intervention study would ideally be an interdisciplinary, multisite, international, NIH-supported trial.

8. Conclusion

Although great strides have been made in understanding ictal semiology, patient characteristics, and diagnosis with video/EEG monitoring, validated treatments and controlled trials are lacking. Neurologists, psychiatrists, psychologists, and emergency departments are aware of the difficulty in treating patients with NES. Estimates are that 10 to 50% of patients with “intractable epilepsy” have either lone NES or a combination of epileptic and nonepileptic seizures. Many patients experience significant medical, family, vocational, and societal consequences of their disorder. This underscores the need for effective, tested treatments for NES.

The participants at this multidisciplinary, international NES Treatment Workshop assessed the state of the science and laid the groundwork to fill the treatment void. The goals were addressed through discussion topics, which focused on: NES in children; presenting the diagnosis of NES; classification of NES subtypes; outcome measures for NES trials; and lastly, pharmacological treatment approaches and psychotherapies, such as cognitive-behavioral therapy, hypnosis, and group and family therapies. The intent was to develop specific research strategies that can be expanded to involve a large segment of the epilepsy and psychiatric treatment communities. The workshop generated recommendations for studying existing interventions and developing novel therapeutic interventions.

Several potential studies emerged from the breakout sessions. These included: (1) a retrospective review of histories of children diagnosed with NES, combined with a prospective collection of information on behavior, cognitive testing, school performance, and psychosocial environment; (2) a multisite interrater reliability study to evaluate the reliability of diagnosis using video/EEG monitoring; (3) a multicenter observational study to identify which approach to presenting the NES diagnosis is most likely to result in treatment compliance; (4) a survey of comprehensive epilepsy centers to determine if there is a therapeutic standard of care; and (5) a three-armed, randomized, clinical trial to test the efficacy of current treatments.

The workshop illustrated the need for collaborative research efforts among those treating patients with NES. Dissemination of workshop results may increase the knowledge of NES and foster further treatment protocols. Along with the publication of this summary, the results of these preliminary discussions were presented at the NES Special Interest Group at the AES meeting in December 2005, and are being presented at meetings of psychiatric and nursing societies as well. Those attending and sponsoring the workshop considered this an important first step in a concerted effort to find effective treatments for patients with NES.

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