The Treatment of Nonepileptic Seizures: Historical Perspectives and Future Directions

*W. Curt LaFrance, Jr. and †Orrin Devinsky

*Brown Medical School, Rhode Island Hospital, Departments of Psychiatry and Neurology, Providence, Rhode Island; and †New York University School of Medicine, Comprehensive Epilepsy Program, NYU Mt. Sinai Medical Center, New York, New York, U.S.A.

Summary: Nonepileptic seizures (NES) are neuropsychiatric disorders presenting with a combination of neurologic signs and underlying psychological conflicts. For more than a century, the medical community has accumulated data and insights about the phenomenology, epidemiology, risks, comorbidities, and prognosis of NES. However, we have not progressed much beyond anecdotal reports of treatments for NES, and no randomized, controlled trials of treatment for the disorder have been conducted. We review the diagnosis and treatment of NES and suggest directions for future research in these areas. Key Words: Nonepileptic seizures—Psychogenic—Pseudoseizures—Pseudoepilepsy—Hysterical seizures—Nonepileptic attack disorder—Diagnosis—Video EEG—Psychotherapy—Pharmacotherapy—Combined treatment—Serotonin.

Nonepileptic seizures (NES) resemble epileptic seizures in that they can present as a sudden, involuntary, time-limited alteration in behavior, motor activity, autonomic function, consciousness, or sensation. However, unlike epilepsy, NES do not result from epileptogenic pathology and are not accompanied by an epileptiform electrographic ictal pattern. The presentation of this neuropsychiatric syndrome has fascinated and confounded neurologists and psychiatrists for centuries. As the divided fields of neurology and psychiatry are being reunified, a joint perspective of the mind/brain conceptualization is gaining prominence (1). An increasing understanding of the paroxysmal disorders in neurology and psychiatry is one of the commonalities shared between the currently dichotomized disciplines. These disorders include migraine, stroke/transient ischemic attack, epilepsy, tics, bipolar/mood disorders, and panic disorder, in which symptoms and signs present acutely or subacutely and then remit. The decade of the brain brought great therapeutic advances for many of these disorders. Nonepileptic seizures, which are commonly occurring paroxysmal disorders, are still situated in the gap between neurology and psychiatry, and treatment remains poorly studied. Also known as pseudoseizures and hysterical seizures, and by many other names in years past (2), NES have been in the medical literature for more than two and a half centuries (3).

An explosion of NES knowledge occurred beginning in the 1980s largely because of the growing use of intensive video-electroencephalographic monitoring (vEEG) (4–7). A recent article reviewing the diagnostic tests, including EEG, neuroimaging, prolactin levels, and personality testing, provides the sensitivities and specificities for each of these tests (8). The gold standard for NES diagnosis remains vEEG. Despite diagnostic advances, there is no standardized, effective treatment for NES. Even as our knowledge of NES phenomenology continues to grow, no randomized, controlled trials for NES treatments have been undertaken.

In contrast to the rapid advances in therapy for epilepsy, stroke, and mood and anxiety disorders, there have been no significant advances made in NES treatment. The lack of “ownership” for NES is a major factor accounting for the lack of therapeutic studies and advances. Although stroke, seizure, and migraine have a home in neurology, and mood and anxiety disorders have a home in mental health practice, no discipline has “claimed” NES. This disorder is best diagnosed by neurologists with expertise in clinical neurophysiology by long-term monitoring and vEEG, and then best treated by psychiatrists or psychologists whose experience affords them a familiarity with psychological constructs and conflicts. This borderland diagnosis leaves many patients improperly diagnosed or inappropriately treated. Even when correctly diagnosed, many times the only therapy offered to patients is the
recommendation to see a mental health care provider; then they are often lost to follow-up (9).

On referral for treatment, many psychiatrists and psychologists may doubt the diagnosis and communicate mixed messages to the patient (10,11). These mixed messages, in combination with a patient’s perception and understanding of his or her NES after diagnosis, greatly affect outcome and functioning (12).

We can use other neurologic disorders, such as stroke, as an analogy to better understand NES. Because both are paroxysmal disorders, comparing types of stroke and treatments aid in proposing a neuropsychiatric model for NES semiology and treatment. The treatment of paroxysmal disorders in both neurology and psychiatry uses symptomatic and prophylactic treatment. In stroke we use thrombolitics to treat the acute event—a “clot buster” can have immediate effects on the pathophysiology of ischemic cerebrovascular disease. Another means of treating stroke is stroke prevention. By treating the risk factors for and precursors of stroke (atrial fibrillation, hypertension, diabetes mellitus, and smoking), we decrease the incidence of stroke.

For psychogenic seizures, no established “NES-olytic” exists. Although we have symptomatic treatment for stroke, we have none for NES. Although psychobiology and functional neuroanatomy may be associated with NES (13), our current understanding of the underlying cause of NES is psychological (14). In psychiatric disorders, we have two main treatments for “prophylaxis”—psychotherapies and somatic therapies. Just as aggressive management of hypertension and diabetes decreases stroke, case reports suggest that appropriately addressing the psychological issues and the psychiatric comorbid diagnoses may reduce NES (15). Psychotherapy addresses the underlying psychological issues. Therapy and psychopharmacology aid in treating the comorbid psychiatric diagnoses. This prophylactic approach to the paroxysmal neuropsychiatric disorder NES is the basis of the current research on NES reduction and improvement of patient health being conducted in our neuropsychiatry of epilepsy program. Distinguishing the psychogenic components and behaviors of NES will also improve epilepsy care in those who have mixed nonepileptic and epileptic seizures.

The diagnosis of NES is often seen as a unitary disorder or syndrome. Just as the behavioral manifestations of NES vary tremendously, the underlying etiologies are also varied. There are many etiologies for right hemiparesis with aphasia in a stroke patient (e.g., atrial fibrillation–induced cardioembolic ischemic stroke, amyloid angiopathy, or tumor with hemorrhagic necrosis). Similarly, there are potentially many etiologies for NES. Precursors of psychogenic NES include childhood sexual abuse, physical abuse, comorbid psychiatric conditions, minor head trauma, disability claims, and reinforced behavioral patterns, among others. In identifying signs, symptoms, and situations that are associated with NES in a patient, we can then provide interventions to promote the mental, physical, and social health of the patient (16).

**HISTORICAL ASPECTS OF NES TREATMENT**

Hysteria and epilepsy have been recognized and linked by medical practitioners since ancient times (17). Mandeville recorded the first full description of a hysterical seizure (3). In 1730, he wrote: “As to Fits, some are seiz’d with violent Coughs; others with Hickups; and abundance of Women are taken with Convulsive laughing. There are Fits that have short Remissions, in which you would think the Woman was going to recover, and yet last many Hours. Some are so slight that the Patients only lose the Use of their Legs and Tongue, but remain sensible; others again are so violent that those who are seiz’d with them, foam at the Mouth, rave and beat their Heads against the Ground; but whether they resemble an Apoplex, or are only fainting, or seem to be Epileptick, they all come under the Denomination of Hysterick . . . .”

In a dialogue between a physician and a patient whose daughter also suffers from hysterical convulsions, Mandeville also records the first prescription for NES: Philopirio, a physician. “. . . wherefore if the Lady’s Youth and Strength be prudently assisted, I am of the Opinion, Madam, that she’ll certainly be cured. In order to it, in the first Place, I would for one Month prescribe a Course of Exercise, and no Medicines at all.” Polytheca, a patient.

“A Course of Exercise! and no Medicines at all!” Interestingly, the patient’s dismay at a physician’s prescribing behavioral methods and not prescribing a medicine to take away the nonepileptic spells is found similarly, even three centuries later.

In the late 19th century, the neuropsychiatric syndrome of NES was established in the medical literature (referred to as hystero-epilepsy). Briquet, Charcot, Richer, and Gowers described NES, but the French and English differed in treatment approaches (18–21). Charcot, with his understanding of hypnosis, probably used the power of suggestion, and he promoted ovarian compression for treatment of acute attacks. Gowers endorsed aversive therapies such as closing the nose and mouth, faradization (electric shock to the skin), and hydrotherapy. Long-term management for both men consisted of environmental changes with removal from the home, suggesting that family dysfunction can influence NES recurrence.

Gowers documented his recommendations for treatment of NES in 1881 (22). The 1901 second edition of Gowers’ monograph on epilepsy updates treatment of hysteroid attacks: “. . . the most important point is abstinence from that to which there is an invariable tendency—restraint. All restraint intensifies the struggling movements which are the object of restraint.” If the attacks
do not cease in a few minutes, “it may be desirable to cut them short. This can often be effected by a strong sensory impression of any kind . . . such as a strong induced current applied to one of the limbs. A magnetoelectric apparatus answers well.” He also described the intelligible utility of “a vigorous tug at the pubic hair” in the treatment armamentarium. “Affusion with water is often employed, but more than one jugful is generally needed. A small quantity will suffice, if poured into the mouth of the patient.””

“Closing the mouth and nose with a towel until the patient is on the point of asphyxia, when all convulsion ceases,” was noted as expedient; however, he acknowledged that “the chief disadvantage of this method is the impression it conveys to the friends.” Finally, “the most effective measure of arresting severe attacks, which would otherwise go on for an hour or two, is the injection of apomorphia. After injection of one sixth of a grain, he observed, “in two minutes all spasms ceased, and the patient began to look uncomfortable. In three minutes got up and walked to the nearest sink; and in four minutes vomited copiously”” (23).

Charcot’s ovarian compression methods were not as readily accepted in the United States as they were in Europe, as noted in a letter to the American Journal of Insanity. “In many of Charcot’s cases of grave hysteria, ovarian pain and tenderness have been marked features; and the

Professor lays great stress upon the occurrence of such symptoms, and upon the fact that firm ovarian pressure will, in hystero-epilepsy, arrest the paroxysms. Our experience does not coincide with this. In the case of hystero-epilepsy spoken of above, ovarian pressure did not arrest the fits; and this is our common experience. In American women, the ovaries do not seem to be often involved in hysteria, nor are we able to feel them or impress them by the method described by Charcot. Often, too, I have seen very marked ovralgia and ovarian tenderness, without hysterical symptoms” (24).

Although our treatments are refined in the sense that we psychopharmacologically target neurotransmitter abnormalities in patients or treat them with individualized psychotherapies, after >200 years, we have not added one controlled trial to empirically test the outcome of our treatments for NES. Despite this, we can learn about NES treatment from the numerous case reports, case series, and retrospective treatment reports.

The NES psychotherapy data include case reports, small uncontrolled trials, or medium-size retrospective follow-up studies. We reviewed all of the NES treatment literature and included the articles that gave clear descriptions of their treatment(s) and the individual/population treated in Table 1. (Where repeated treatment descriptions in case reports were found, we included only the earliest noted

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Treatment</th>
<th>Design</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aboukasm et al., 1998 (25)</td>
<td>61</td>
<td>“Supportive confrontation,” P</td>
<td>Observational, retrospective, nonrandomized, with control group, telephone follow-up</td>
<td>III</td>
</tr>
<tr>
<td>Lambert and Rees, 1944 (26)</td>
<td>17</td>
<td>IVB, P, OT, E, H</td>
<td>Observational, retrospective, nonrandomized</td>
<td>IV</td>
</tr>
<tr>
<td>Ramani and Gumit, 1982 (27)</td>
<td>9</td>
<td>Inpatient, BT, BM, short-term PdP, FT, OT</td>
<td>Uncontrolled, unblinded, telephone follow-up</td>
<td>IV</td>
</tr>
<tr>
<td>McDade and Brown, 1992 (28)</td>
<td>16</td>
<td>ST, OT, OC, AMT, PT, FT</td>
<td>Prospective, uncontrolled, unblinded</td>
<td>IV</td>
</tr>
<tr>
<td>Betts and Boden, 1992 (29)</td>
<td>121</td>
<td>OC, CBT, H, P, FT, MT</td>
<td>Chart review, retrospective</td>
<td>IV</td>
</tr>
<tr>
<td>Buchanan and Snars, 1993 (30)</td>
<td>50</td>
<td>“Direct communication,” P, PdP, ST</td>
<td>Chart review, retrospective</td>
<td>IV</td>
</tr>
<tr>
<td>Kim et al., 1998 (31)</td>
<td>14</td>
<td>Inpatient psychotherapy H, GT, IT, FT</td>
<td>Chart review, uncontrolled, telephone follow-up</td>
<td>IV</td>
</tr>
<tr>
<td>Rusch et al., 2001 (32)</td>
<td>26</td>
<td>CBT, IT, PdP, OC</td>
<td>Uncontrolled, unblinded</td>
<td>IV</td>
</tr>
<tr>
<td>Gardner, 1967 (33)</td>
<td>1</td>
<td>Parental contingency management plan</td>
<td>Case report</td>
<td>IV</td>
</tr>
<tr>
<td>Gardner, 1973 (34)</td>
<td>1</td>
<td>H</td>
<td>Case report</td>
<td>IV</td>
</tr>
<tr>
<td>Iowa and Lorentzson, 1976 (35)</td>
<td>1</td>
<td>OC with patient</td>
<td>Case report</td>
<td>IV</td>
</tr>
<tr>
<td>Parraga and Kashani, 1981 (36)</td>
<td>1</td>
<td>PdP, OC, H, OT</td>
<td>Case report</td>
<td>IV</td>
</tr>
<tr>
<td>Miller, 1983 (37)</td>
<td>3</td>
<td>H</td>
<td>Case series</td>
<td>IV</td>
</tr>
<tr>
<td>Aybward, 1984 (38)</td>
<td>2</td>
<td>CBT, ST, FT</td>
<td>Case report</td>
<td>IV</td>
</tr>
<tr>
<td>Shulman and Silver, 1985 (39)</td>
<td>1</td>
<td>TCA and PdP</td>
<td>Case series with comparison group</td>
<td>IV</td>
</tr>
<tr>
<td>Mims and Antonello, 1994 (40)</td>
<td>3</td>
<td>IT, FT, E</td>
<td>Case report</td>
<td>IV</td>
</tr>
<tr>
<td>Baker et al., 1995 (41)</td>
<td>1</td>
<td>FT</td>
<td>Case report</td>
<td>IV</td>
</tr>
<tr>
<td>Swingle, 1998 (42)</td>
<td>3</td>
<td>Neurofeedback, P</td>
<td>Case series</td>
<td>IV</td>
</tr>
<tr>
<td>Blumer, 2000 (43)</td>
<td>Unspecified</td>
<td>Various medications, P</td>
<td>Chapter report</td>
<td>IV</td>
</tr>
<tr>
<td>Chand and al Khaliili, 2000 (45)</td>
<td>1</td>
<td>Graded exposure</td>
<td>Case report</td>
<td>IV</td>
</tr>
</tbody>
</table>

NES, nonepileptic seizures; CEP, comprehensive epilepsy program; P, psychotherapy; N, neurologist; IVB, intravenous barbiturate; OT, occupational therapy; E, education; H, hypnosis; BT, behavioral therapy; BM, behavioral modification; PdP, psychodynamic psychotherapy; FT, family therapy; ST, supportive psychotherapy; OC, operant conditioning; AMT, art and music therapy; PT, physical therapy; CBT, cognitive behavioral therapy; MT, major tranquilizer (antipsychotic); GT, group therapy; IT, individual psychotherapy; TCA, tricyclic antidepressant.

Epilepsia, Vol. 45, Suppl. 2, 2004
article.) All of the treatment trials for NES to date would be considered class IV data with the exception of one class III retrospective study that used a control group (44). Outcomes in these reports are discussed as follows.

In the review, we could find only one reference to a prospective series in the NES treatment literature. McDade and Brown (28) reported on an uncontrolled therapeutic program with 16 patients with NES who completed an individualized treatment program consisting of supportive psychotherapy, occupational therapy, and operant conditioning, with some individuals receiving art and music therapy, physiotherapy, AED reduction, and family therapy when indicated. Treatments lasted an average of 12 weeks, and half of the patients had NES cessation at the end of treatment. Kim et al. (31) performed a telephone interview with 14 patients with NES who underwent inpatient psychiatric treatment after vEEG diagnosis of NES. They reported that 11 of 14 patients (79%) experienced cessation or significant improvement after receiving a combination of hypnosis, group therapy, family therapy, and individual therapy. The inpatient series report success from a “shotgun” approach with a combination of therapies and milieus. Rusch et al. (32) found that matching specific psychotherapies to the patient’s comorbid diagnoses produced greater seizure-free rates, with 21 of 33 patients (63%) reaching event-free status at the end of treatment.

The pharmacologic references for NES treatment using intravenous barbiturates, tricyclic antidepressants, selective serotonin reuptake inhibitors, β-blockers, analgesics, or benzodiazepines are anecdotal references in case reports, journal review articles, or book chapters (26,39,43,45,46).

Reported outcomes in NES treatment vary from greatly successful to not impressive. The higher success rates are noted in the articles and chapters describing longer inpatient admissions where patients were managed by a multidisciplinary team familiar with NES (27). More recent reviews, however, reveal that roughly one third of the patients have NES cessation, and another third have a reduction in their NES (47). However, quality of life measures improve when patients reach NES freedom, and not when their NES are merely reduced (48). Even with NES improvement, up to half of the patients remain on government or family support and are unemployed (49), and patients with NES generally do not expect to return to work (50). One study found that patients with NES scored higher on hypochondriasis and somatic-complaint scales of the Minnesota Multiphasic Personality Inventory when compared with patients with epilepsy, reflective of a focus on bodily function and neurologic complaints (51). Poor quality of life in patients with NES may partly result from their somatic focus. A factor analysis of predictors of health-related quality of life revealed that patients with NES had more bodily concern than those with epilepsy (52), and that somatic focus may influence health-related quality of life.

It was once thought that absence of physical injury sustained during a seizure was a diagnostic indicator differentiating NES from epileptic seizures; however, more than half of all patients with NES actually have physical injury associated with their NES (53). Iatrogenic issues are also prevalent in NES, as up to half of NES patients have had “pseudo-status,” and 27.8% of patients with NES are admitted to intensive care units inappropriately for treatment (54).

**RESEARCH IN NES**

Future directions for NES research are in three major areas: diagnosis, prevention, and treatment.

**Diagnosis**

There are different subtypes of NES, and diagnosis of the subtype may be as important as making the vEEG diagnosis of NES for directing appropriate treatment. Psychologists have helped to better classify types of NES into posttraumatic NES or developmental NES, on the basis of etiology (55). Posttraumatic NES are thought to develop in response to acute or chronic exposure to traumatic experiences, such as physical or psychological trauma and sexual or physical abuse. Developmental NES arise from difficulties coping with tasks and milestones along the individual’s continuum of psychosocial development.

Glosser et al. (56) developed a 20-min structured interview sampling 14 risk factors, which discriminated well between psychogenic NES and intractable epilepsy. A discriminant function analysis revealed that the presence of four of the 14 risk factors correctly classified NES patients with an 88.3% sensitivity. On the basis of the classifications developed by Martin and Gates (57), we are developing a semistructured clinical interview for diagnosis NES module for more specific diagnosis of NES subtypes. This information may help select appropriate treatment for NES subtypes and improve outcomes (32).

**Prevention**

Preventive measures may assist in reducing NES development and frequency. Risk factors for NES have been outlined by various authors (58–60). Reuber et al. (61) compared 90 patients with mixed NES and epilepsy to 90 patients with epilepsy and described risk factors for developing NES in patients with epilepsy. The prevention approach would address two main questions: (a) What risk factors promote the development of NES? (b) What risk or protective factors contribute to NES cessation in the diagnosed and treated groups of patients? To address the latter, Kanner et al. (62) used logistic regression to assess neurologic and psychiatric variables and found various psychiatric factors to be predictors of outcomes of NES recurrence.
Primary, secondary, and tertiary prevention measures in NES can be modeled after risk templates in other disorders. For example, Malaspina outlines risks for developing schizophrenia through a combination of environmental exposures: epigenetic mechanisms, including cognitive, emotional, and behavioral influences; and critical neurodevelopmental periods for genomic programming (63). Prevention and treatment involves examining multiple levels, from the whole “system” in which the patient and family exist, down to neuronal mechanisms (Fig. 1). This model underscores the need for communication between the various system members as being essential for patient health.

Treatment

Treatment of NES has been reviewed many times (16,61–64). Although we can learn much from prior retrospective reports, it is essential that controlled prospective trials of pharmacologic, psychotherapeutic, and combined treatment be conducted. The notion that presenting the diagnosis of NES to a patient is enough to terminate NES has been proposed, and a protocol for a direct, nonpejorative relaying of the diagnosis is given by Shen et al. (65). One retrospective study compared the number of NES in the 24-h periods before and after vEEG diagnosis using the Shen protocol and found that 18 of 22 patients (82%) with NES had a reduction in their NES frequency in that day’s time (66). Buchanan and Snares (30) found that “direct communication of the diagnosis” of NES led to cessation in 15 of 18 patients (83%) with “acute or situational” NES. However, giving the diagnosis does not effectively treat the large majority of patients with chronic NES, as many patients experience the recurrence of NES in the period after diagnosis (67). The understanding and acceptance of the diagnosis contribute to their outcomes (64,68). In many cases, however, even after the diagnosis is presented in a supportive and educational manner, NES continue. Furthermore, the disability associated with NES often persists even with NES cessation (69).

The National Institute of Neurological Disorders and Stroke is funding a pilot randomized, controlled trial of a selective serotonin reuptake inhibitor for patients with NES, which is being conducted currently. This treatment paradigm is based on the approach of treating comorbid psychiatric disorders associated with NES. Depression, anxiety, and impulsivity are documented in NES, and treating these serotonergic-mediated disorders may reduce NES. The pharmacologic trials will be followed by psychotherapy trials addressing cognitive patterns and family dysfunction, areas that have been shown to be affected in patients with NES and their family members (49,70). After the individual trials, combined-treatment trials of pharmacology and psychotherapy may reveal synergistic effects in the treatment of patients with NES.

CONCLUSION

Nonepileptic seizures commonly occur and are frequently seen by neurologists, psychiatrists, and emergency department physicians. We know much about the phenomenology of the disorder, but we lack knowledge of specific treatments. While the disorder is treatable, an effective treatment that yields long-term NES freedom and improved quality of life has yet to be discovered. Prior treatment reports reveal that coordination between neurologists and psychiatrists/psychologists, with accurate diagnosis and prompt initiation of psychotherapy and communication between care providers, patient, and family,
yields higher treatment success. Pharmacologic treatment of the commonly occurring comorbid psychiatric disorders, along with diagnosis-directed psychotherapy, may be the key to improving outcomes in these patients. Therapy will probably need to be individualized based on etiology, level of intelligence, family dynamics, comorbid psychiatric illness, and other factors. Controlled trials of NES treatments are greatly needed.

Acknowledgment: This work was supported by grant 1K23-NS 45902-01 from the National Institute of Neurological Disorders and Stroke.

REFERENCES


70. Dinneen C, Delanty N, O’Keane V, Meaney AM, MacKin D. Patients with nonepileptic seizures show higher levels of alexithymia, emotional control, and stressful adult experiences than do patients with epilepsy and matched controls. Epilepsia 2001;42(suppl 7):137–8.