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Review

Behavioral intervention as an add-on therapy in epilepsy: Designing a clinical trial

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ABSTRACT

Many patients with epilepsy continue to experience seizures despite taking medication, and stress is a commonly reported trigger for seizures in these individuals. Therefore, a behavioral therapy proven to be effective in epilepsy could be a valuable adjunct to current pharmacotherapy. The challenges in testing such a behavioral intervention for epilepsy are numerous, including lack of consensus about sham designs, maintaining the blind, and powering the study absent known effect sizes. Herein, we present the design of a randomized, controlled, double-blind trial of progressive muscle relaxation as an add-on therapy for refractory epilepsy. Progressive muscle relaxation, which involves the tensing and releasing of muscle groups one at a time, is a well-established technique that relaxes the body and mind, reduces stress, and may improve seizure control. Study design issues discussed may provide insights that will inform future behavioral research in epilepsy.

1. Introduction

Despite advances in pharmacotherapy, up to 30% of patients with epilepsy continue to experience seizures while taking medication [1,2]. Since 1993, twelve new antiepileptic drugs (AEDs) have been approved in the US yet the burden of refractory epilepsy persists. Though AEDs offer tremendous benefits, seizure control is often incomplete and medications have adverse effects as well as drug–drug interactions. Effective behavioral treatments would be a valuable adjunct to current pharmacotherapy. Behavioral treatments for epilepsy have been discussed since 1977 [3], but have not been subjected to investigation in large clinical trials. In a recent review of drug-resistant epilepsy treatment in the New England Journal of Medicine, Kwan et al. commented that "to date, no complementary or alternative therapy has been shown to be effective for epilepsy in multi-center, double-blind, controlled trials" [4].

Candidate behavioral interventions for epilepsy have included progressive muscle relaxation, biofeedback, cognitive behavioral therapy, and Acceptance and Commitment Therapy (ACT) among others [5]. Subjecting these behavioral interventions to a rigorous clinical trial poses many challenges. Previous studies have been limited by many shortcomings, most importantly the use of observational designs rather than randomized and blinded controlled trials. In addition, small sample sizes, changes in medication during treatment, and imperfect ascertainment of seizure outcomes make causal inferences difficult. Moreover, these approaches have not targeted specific seizure triggers, but rather focused on a general non-medication approach.

Recent evidence from both paper and electronic diary studies suggests that an increase in reported stress is associated with a higher probability of seizures within the next 12–24 h [6–8]. Since perceived stress is well managed through behavioral interventions, stress management may be a useful adjunctive treatment for epilepsy in persons with stress as a provocative factor. Such a behavioral intervention targeting stress reduction could provide an accessible, safe and low cost approach for ameliorating medication-resistant epilepsy.

This manuscript describes the background and design considerations for a recently launched study, Stress Management Intervention for Living with Epilepsy (SMILE). First we present a brief review of the evidence that stress is a provocative factor in epilepsy using data from both experimental models and human observational studies. Next, we review previous trials of stress management in epilepsy, highlighting strengths and weaknesses. Finally, we describe our approach to the design of a randomized, controlled, double-blind study of progressive muscle relaxation, a behavioral stress reduction technique, as an add-on therapy for patients with refractory epilepsy. This review is intended to reinvigorate the discussion and exploration of behavioral treatments for medication-resistant epilepsy.

2. Stress and epilepsy: a complex relationship

Understanding the role that stress plays in epileptic disorders is complex and requires an exhaustive review beyond the scope of this

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paper. However, for the purposes of designing a clinical trial, it is important to recognize that stress may have a role as a risk factor for the development of epilepsy, may be a trigger for the occurrence of seizures in a person with epilepsy, may exacerbate seizure frequency, and/or may be an important component of a prodrome preceding a seizure.

Prior to examining the role of stress in epilepsy, an important challenge lies first in defining stress itself. Stress is a term that is commonly used but is not straightforward to define. Seyle first documented the ambiguity of the term, citing stress in a biological context as "the non-specific response of the body to any demand placed upon it" [9]. Neuroscientists currently limit the definition of stress to "conditions where an environmental demand exceeds the natural regulatory capacity of an organism, in particular situations that include unpredictability and uncontrollability" [10]. There is no matching definition for use in clinical studies, and when subjects endorse "stress" as a factor in their seizures, it is likely that stress has a different meaning to different people. Recognizing this fact, when subjects are asked to rate their stress level in a clinical study, it may be necessary to analyze change in stress for each individual rather than look at absolute values of stress.

Stress has been shown to be an independent risk factor for the development of epilepsy. Persons exposed to sub-acute or chronic stressful conditions such as active army duty or the loss of a child appear more likely to develop epilepsy than those in less stressful scenarios [11,12]. Stress has also been demonstrated to be a trigger factor, or precipitant, as well as an exacerbating factor for seizure occurrence in persons with epilepsy [7,13–22]. Trigger factors increase the probability of seizure over a relatively short time period, usually hours to a couple of days, while exacerbating factors increase the probability of seizures over longer periods of time, often days to weeks.

Studies of stress and epilepsy are varied, ranging from questionnaire to prospective diary studies, and examine stress in relation to major life events and/or daily minor stress. In questionnaire studies, stress is endorsed as a trigger, or precipitant, by more than 50% of people with epilepsy [20,23], while major life events are associated with seizure exacerbation in 8% to 50% of patients [6,12,24,25]. In prospective diary studies, both daily stress and stressful life events have been linked to increased seizure frequency [7,13,17,26,27]. For example, Temkin and Davis [26] and Haut et al. [7] reported that risk of seizure increased in relation to increases in reported daily stress levels, while Neugebauer [17] showed that stressful major life events led to an increase in seizure occurrence.

A major deterrent to the use of stress management in epilepsy is the time window from exposure to seizure. Data from a paper diary study with once daily data collection indicated an increase in the risk of seizure within 24 h of higher stress; this time window was narrowed to 12 h in a follow-up electronic diary study with twice daily data collection [8]. In studying trigger factors, individual cases can also be informative. For example, Gilboa [28] reported a child who had seizures triggered by emotional stress involving conflict with her mother over a 2-hour period during observation in an epilepsy monitoring unit. Electroencephalography revealed that the child had three electroclinical seizures in 30 min, with each occurring 30–90 s after a conflict.

Despite the increasing body of literature linking stress as a causal trigger for seizure occurrence, it is important to recognize a potential limitation in this approach. The report of stress in the hours preceding a seizure may in fact represent a prodromal state, as has been reported in many studies [8,20,29]. If stress is indeed a premonitory or prodromal feature and not a trigger, then a stress reduction intervention may not succeed. Determining the true nature of this complex relationship will likely require integration of subjective (diary) and objective (biological) data.

While an increasing body of literature supports the relationship between stress and seizure occurrence, it is clear that there is an immediate need for exploring this relationship further. As discussed above, stress may be a direct trigger for seizures, in which case stress reduction interventions may be effective in reducing seizure frequency. With this need in mind, the current clinical trial was designed.

3. Stress management and epilepsy

There is strong preliminary evidence for the effectiveness of stress management techniques for people with epilepsy (Table 1). In particular, progressive muscle relaxation (PMR), which involves the tensing and releasing of muscle groups one at a time, is a well-defined technique that has demonstrated effectiveness for stress reduction [30,31]. Progressive muscle relaxation has been used as an adjunctive treatment in observational studies in epilepsy with promising results. Additionally, several studies have examined PMR in people with epilepsy experimentally. Rousseau et al. [32] compared three weeks of PMR versus a control arm of quiet sitting in 8 adults with epilepsy. After this 3-week period, the control group then practiced the true PMR for three weeks. All 8 subjects experienced a decrease in seizure frequency from baseline to treatment and reported improvements in well-being as well.

Dahl et al. [33] divided 18 adults with refractory epilepsy into three groups — contingent relaxation, attention control, and a no-treatment control group for a 6-week intervention. The contingent relaxation involved learning to apply progressive muscle relaxation to situations and feelings associated with a high risk of seizure activity. Results showed a significant reduction only for those patients receiving the contingent relaxation treatment.

Finally, Puskarich et al. [34] compared six sessions of progressive relaxation training or quiet sitting in 24 adults with epilepsy. The mean decrease in seizure frequency was 29% for the progressive relaxation training group but only 3% for the quiet sitting group.

While the studies described above provide strong supportive evidence for stress management in epilepsy, these studies have certain limitations. The sample sizes are all small, ranging from 8 to 24, and the duration of treatment varies even within the same study. Furthermore, while each had at least one control group, the control groups were not directly matched to the intervention, i.e., quiet sitting, nondirective conversation, supportive therapy, or wait list control. Blinding may be difficult to maintain with these types of controls, and it is theoretically possible that quiet sitting may induce relaxation and mimic some of the effect of the active intervention. For these reasons, recent studies of PMR outside of epilepsy have attempted to develop

Table 1
Stress reduction interventions for epilepsy.

Study	*N*	Design	Outcome
Rousseau [32]	8	PMR vs sham PMR	Decrease in seizure frequency
Dahl [33]	18	Contingent relaxation (CR), attention control, and no-treatment control	Decrease in seizure frequency for CR group only
Puskarich [34]	24	Progressive relaxation training (PRT) vs quiet sitting	Decrease in seizure frequency: 29% for PRT vs 3% for quiet sitting
Nagai [35]	18	Galvanic skin response biofeedback vs sham biofeedback	Decrease in seizure frequency
Sathyaprabha [36]	34	Yoga vs routine exercises	Decrease in seizure frequency and parasympathetic dysfunction
Lundgren [37]	18	ACT vs yoga	Decrease in seizure frequency in both groups, ACT greater decrease than yoga