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Review

Stress as a seizure precipitant: Identification, associated factors, and treatment options

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ABSTRACT

Stress is a common and important seizure precipitant reported by epilepsy patients. Studies to date have used different methodologies to identify relationships between epilepsy and stress. Several studies have identified anxiety, depression, and childhood trauma as being more common in patients with epilepsy who report stress as a seizure precipitant compared to patients with epilepsy who did not identify stress as a seizure precipitant. In one survey study it was found that a majority of patients with stress-triggered seizures had used some type of stress reduction method on their own and, of those who tried this, an even larger majority felt that these methods improved their seizures. Additionally, small to moderate sized prospective trials, including randomized clinical trials, using general stress reduction methods have shown promise in improving outcomes in patients with epilepsy, but results on seizure frequency have been inconsistent. Based on these studies, we recommend that when clinicians encounter patients who report stress as a seizure precipitant, these patients should be screened for a treatable mood disorder. Furthermore, although seizure reduction with stress reduction methods has not been proven in a randomized controlled trial, other important endpoints like quality of life were improved. Therefore, recommending stress reduction methods to patients with epilepsy appears to be a reasonable low risk adjunctive to standard treatments. The current review highlights the need for future research to help further clarify biological mechanisms of the stress-seizure relationship and emphasizes the need for larger randomized controlled trials to help develop evidence based treatment recommendations for our epilepsy patients.

Epilepsy is a complex condition, where different underlying pathologies cause excessive synchronous neural activity in the brain, resulting in seizures of various clinical semiology, frequencies, and intensities. Patients with epilepsy face many challenges with this condition, but perhaps the most difficult is the unpredictability of seizure occurrence. Furthermore, patients often report specific triggers for seizures by various exogenous and endogenous factors [1–9]. The most common precipitating factor reported by patients is stress [1,6,9–16]. A relationship between stress and epilepsy has been reported dating back to over a half century ago [17–19]. It has been noted that stress can not only increase seizure susceptibility and possibly be another form of reflex epilepsy [20], but also increase the risk of the development of epilepsy, especially when stressors are severe, prolonged, or experienced early in life [1,21]. This manuscript is a thorough literature review of human studies evaluating the relationship between stress and epilepsy.

The earliest studies that evaluated the effects of stress and epilepsy were done in the form of diary studies assessing the relationship between individual stress and seizures. In 1984 Temkin et al. reported a study of 12 adults with epilepsy who used a 3-month diary to document their seizures and stressful life events [22]. The study showed that patients experienced significantly more seizures on 'high-stress days' than 'low-stress days'. Webster et al., looked at the effect of life events on seizures by retrospectively correlating monthly seizure frequency in the past one to six years to experienced life events in 18 epilepsy patients [23]. An association was found between monthly seizure frequency and life events in 3 patients (17%) and a significant

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change in seizure frequency after experiencing a life event in 6 patients (30%). Furthermore, Neugebauer et al. did a prospective study and found a significant increase in seizure frequency within 24 h after an unpleasant event in 5 out of 37 patients (14%) and a significant decrease in 2 (5%) patients [24].

Other early studies evaluated changes on the electroencephalogram (EEG) in response to stressful verbal stimuli in healthy controls and found that there were subtle EEG changes (narrowing of the bandwidth and regional changes in frequency), but large enough for a blinded reviewer to correctly identify 92% of stress stimuli on EEG [25,26]. Similarly, in epilepsy patients, stressful interviews induced EEG changes (exaggerated spiking, paroxysmal activity, or epileptiform complexes) in the majority [26,27]. There was also a case-series of five patients with epilepsy which demonstrated that stress-inducing audio and video recordings could induce seizures [28].

Other studies looked at events that would be considered stressful to a large population of people and measured the effects on the subset of people who had known epilepsy. For example, a retrospective study investigating the frequency of seizures during the Persian Gulf War looked at 100 Israelis with a previous diagnosis of epilepsy; 82 reported experiencing stress during the war, but only 8 reported an increase in seizures [29]. The authors concluded that there may only be a weak relationship between stressful events and seizures. A controlled study looked at the effects of flood evacuation in the Netherlands in 1995 [30]. Seizure frequency from seizure diaries and medical records were compared in a group of 30 evacuees and 30 control patients before, during, and shortly after evacuation. The two groups differed significantly in the degree of change of seizure frequency from pre-evacuation to the period during evacuation and shortly after. Eight evacuees showed an increase in seizures versus only one control subject and stress was reported in 91.9% as a seizure triggering factor. However, of the evacuees with a change in seizure frequency, only three reported stress as a trigger. In 2002, a study evaluated the occurrence of epileptic seizures during the 1991–1992 war in Croatia on children with epilepsy in war-affected areas and non-war-affected areas [31]. Seventy-two children with epilepsy from the war-affected areas were compared to 39 children with epilepsy from non-war-affected areas. During the war, children from war-affected areas had epileptic seizures more often than children not affected by the war. Additionally, the 10-year follow up showed that patients who had their first epileptic seizure during a time of stress were more likely to have controlled epilepsy or even be off medication years later.

It has also been demonstrated that there is a complex interaction between mood states and stress to trigger seizures. In 2008, a study was performed on new military recruits [32]. The military records of over 300,000 adult men recruited to the Israeli army were used and evaluated for severity of epilepsy and subdivided among different occupational categories. The study found that there was an increased risk of seizure in the combats units compared to the maintenance and administrative units, possibly secondary to the corresponding increase in physical and mental stress. Also, in 2009, subjects were given two consecutive questionnaires on stress and depression in patients with epilepsy and showed that perceived stress levels over the past month predicted times since the last seizures and seizure frequency, both mediated by their depression score [33]. Furthermore, Blanchet et al. reported a decline in mood scale scores for positive and negative mood states (depression, anxiety, freedom, and anger) preceding seizures [34].

A more detailed approach using functional magnetic resonance imaging (fMRI) to assess emotional processing in people with epilepsy was explored by Szaflarski et al. in 2014 [35]. In this study, patients with left temporal lobe epilepsy were evaluated with fMRI with an event-related facial emotion recognition task (happy, sad, fearful, and neutral). Of the 34 patients, 17 were seizure-free, while 17 had frequent seizures. Mood was assessed with the Beck Depression Inventory (BDI) and the Profile of Mood States (POMS). In patients with left temporal lobe epilepsy, fMRI showed decreased blood oxygenation level dependent (BOLD) signal in the hippocampus/parahippocampus and cerebellum when processing happy faces and increased BOLD signal in occipital regions in response to fearful faces and in the left periarcheocortex for neutral faces. Overall, patients with left temporal lobe epilepsy process emotions like the healthy control group. The study also found that patients with left temporal lobe epilepsy with uncontrolled seizures required more significant involvement in processing emotions in certain areas, which was not found in the controlled seizure group, suggesting that there is a significant relationship between seizure control and emotion processing.

Haut et al., studied stress as a seizure trigger in the larger context of seizure precipitants and prodromes [36]. This series of studies asked participants prospectively to evaluate stress daily plus log an assessment of seizure probability in the subsequent 24 h, then correlated these measures with seizure occurrence. The goal was to better identify a pre-ictal state. A total of 19 subjects with localized-related epilepsy used a Palm-based electronic Patient Reported Outcome program, which allowed the subjects to access a questionnaire at regular intervals and answer a set of questions. Information about their emotional state, stress level, perceived stress scale, premonitory features, potential precipitants, sleep, medication adherence, alcohol, and menstruation was documented. Changes in quantitative, self-reported stress (measured on a scale from 1 to 10) were examined in 24 h intervals. Epilepsy localizations were temporal (n = 14); frontal (n = 1); extra-temporal other (n = 2) and non-localizable (n = 2). Each 10-point increase on the happy scale lowered the likelihood of a seizure and a 10-point increase on the nervous scale increased the likelihood of a seizure. Somewhat surprisingly, total stress level, in the PM diaries, was not associated with an increased risk of seizure. Similarly, no item from the perceived stress scale showed an association with seizure outcome. The study overall demonstrated that both changes in mood and other premonitory features contribute to the prediction of seizures over 12 h. Improvements in mood reduced the risk of seizures by approximately 25%. This was a follow up to the previous study done in 2007, which analyzed patient's diary data and, in contrast, found that higher levels of stress and anxiety were associated with a higher risk of having a seizure the next day [37]. Higher levels of stress and anxiety were positively correlated with the likelihood of seizures as well. Limitations of this earlier study included that there was not a standardized scale to measure stress and anxiety and the measures were only taken once daily. Novakova's 2013 review article speculates further about the causal differences between the two studies [15].

Although stress has been implicated as a trigger for epilepsy, few studies have evaluated the idea of stress being a causal factor of the disease. In 2007, as study was done to evaluate the risk of being diagnosed with epilepsy in parents exposed to severe stress caused by loss of a child [38]. Of 21,062 parents who had lost a child in Denmark between 1980 to 1996, it was found that the risk of epilepsy was 50% higher compared to parents who had not lost a child. Furthermore, the risk was increased only during the first 3 years after the loss for fathers, but remained high throughout follow up for up to 18 years with mothers. Additionally, a longitudinal study over 11 years was performed to evaluate exactly the phenomenon of acute stress precipitating epilepsy [39]. The study included patients who reported an emotional shock within three months before the onset of epilepsy (22 out of 4618 consecutive patients). Twelve patients (54%) reported a death

as a trigger, 7 patients (32%) reported that a trusted relationship was broken, and 3 patients (14%) had been subjected to violence (not sexual abuse). The article concluded that stressful life events may contribute to the onset of epilepsy, although it remains an uncommon finding [39].

Neural and physiologic, i.e. cortisol level and heart rate, correlates of the stress response were evaluated by looking at acute psychosocial stress during fMRI stress math task and their relationship with seizure occurrence in patients with left temporal lobe epilepsy [40]. The study hypothesized that when exposed to acute psychosocial stress, patients with left temporal lobe epilepsy would exhibit increases in both hypothalamic-pituitary-adrenal axis (HPA-axis) response and fMRI activation. The study was a cross-sectional analysis involving 23 patients with left temporal lobe epilepsy with normal MRI (other than mesial temporal sclerosis) compared to age- and sex-matched healthy controls. The subjects were administered the 10-item Perceived Stress Scale (PSS-10) and the Beck Depression Inventory-II (BDI-II) before the MRI. The relationship between seizure control and stress perception was also examined. During the fMRI the subjects were given stress tasks, including control math task (non-stressful) and a stress math task. Subjects also provided 1 mL samples of saliva throughout the study to test pre- and post-fMRI salivary cortisol levels which was calculated as a measure of acute stress reactivity (dCORT). The study found that patients with left temporal lobe epilepsy had greater dCORT ($p = 0.048$) and lower BDI-II scores ($p = 0.016$) compared with healthy controls. Patients with poorly controlled epilepsy showed a positive association between seizures frequency and dCORT ($r = 0.73$, $p = 0.016$). fMRI activation to feedback was similar between the groups. Regression analysis revealed no group differences to positive feedback, but compared to the control group, patients with left temporal lobe epilepsy showed decreased activation to negative feedback in several areas of the brain. Overall, this study was the first to characterize the cortical and physiologic responses to acute psychosocial stress and to show a significant relationship between seizure control in left temporal lobe epilepsy and HPA-axis and fMRI signal reactivity to acute psychosocial stress.

The acute stress response was also evaluated in children with epilepsy, ages 6–17 with 64 patients with epilepsy and 40 control subjects [41]. The patients were initially evaluated with questionnaires and a diary assessment for evaluation of stress and seizures. Subsequently, they were exposed to a standardized acute psychosocial stressor (the Trier Social Stress Test for Children), during which salivary cortisol and sympathetic parameters were measured. Of the children with epilepsy, 49% reported acute stress-triggered seizures and the diary analysis showed a positive association between acute stress and seizures. Children with stress-triggered seizures (determined by the questionnaire or diary study) showed a blunted cortisol response to stress compared with patients without acute stress-triggered seizures. The results supported that stress-triggered seizures are associated with alterations of the stress response.

Privitera et al. surveyed a large sample of people in a tertiary epilepsy center to further characterize epilepsy patients who reported stress as a seizure precipitant [16]. Information was collected about the patients' antiepileptic drugs, history of depression and anxiety disorder, prior or current treatment for depression or anxiety, and scores on the Neurological Disorders Depression Inventor (NDDI-E) and Generalized Anxiety Diorders-7 (GAD-7) scales, which had been routinely administered at every clinical visit at the center. Patients were also asked if they felt that they could predict their seizures to determine if stress as a seizure precipitant was correlated with seizure self-prediction. 266 subjects were included, in which 219 of them reported stress-triggered seizures and 47 did not. This prevalence of stress-triggered seizures may reflect the fact that many patients who did not feel that stress triggered their seizures were not interested in participating in the study and filling out the questionnaires. The findings were unclear in determining if acute stress ("minutes to hours") was a more common precipitant than chronic stress ("days to months")—85% of the stress-triggered seizure subjects endorsed chronic stress as a seizure precipitant and 68% felt that acute stress was a seizure precipitant. Of those who endorsed stress as a trigger, 57% had used some type of stress reduction method and, of those who tried this, 88% felt that these methods improved their seizures. A higher GAD-7 score was the only factor that significantly differentiated between those who reported stress as a trigger compared to those who did not ($p = 0.017$). Additionally, the stress-triggered seizure group were more likely to report an ability to self-predict seizures ($p < 0.001$). This study confirmed that stress is commonly reported as a seizure precipitant, whether acute or chronic. The authors felt the most surprising finding was that patients who have stress-triggered seizures often seek stress-reduction methods on their own to self-treat their epilepsy and report high success rates.

More recently, Lee et al. further evaluated the same population from the Epilepsy Center at the University of Cincinnati Neuroscience Institute for early childhood trauma as a risk factor for stress-triggered seizures [42]. All 236 participants in the Privitera et al. study [16] received a Childhood Trauma Questionnaire Short Form (CTQ-SF) through the mail and 119 subjects returned this on paper or electronically. The CTQ-SF is a 28-question scale that evaluates 5 domains of childhood adversity: physical abuse, physical neglect, emotional abuse, emotional neglect, and sexual abuse. Total CTQ-SF score and domain scores were compared between the stress-triggered group and the non-stress-triggered seizure group. Response rates were 91/195 (47%) in the stress-triggered group and 28/41 (68%) in the non-stress-triggered group. There was no significant difference response rate between the two groups and there were no statistically significant differences for types of trauma, although the stress-triggered group had higher sexual ($p = 0.047$) and emotional ($p = 0.06$) abuse scores. Depression and anxiety scores were higher in the stress-triggered group, and as in the prior study, anxiety was still the only independent factor associated with the stress-triggered group in the multivariate analysis ($p = 0.0021$). This study concluded that patients with stress-triggered seizures are more likely to endorse a history of childhood trauma, particularly emotional abuse. It also made the point that 'while stress has been recognized as one the most frequent precipitants of seizures in patients with epilepsy, exploring the relationship between stress and seizure control has been challenging due to the conceptual, phenomenologic, and etiologic heterogenicity of "stress"' [42].

A case-control study evaluated the degree of perceived stress in epilepsy patients who perceived stress as a seizure precipitant [43]. Adult epilepsy patients requiring at least one year of treatment with an anti-epileptic drug (AED) who consecutively visited the epilepsy clinic over a six-month period were included. Age-and sex-matched subjects without a history of loss of consciousness or epileptic seizures were used as controls. The patients were divided into three groups per their seizure control: well-controlled epilepsy (at least one-year seizure free), poorly controlled epilepsy (did not meet criteria for the other two groups), and uncontrolled epilepsy (failure in adequate trials of 2 AEDs with an average of more than one seizure per month for 18 months and no seizure-free periods longer than 3 months). The patients completed several self-report questionnaires, including the Korean version of the Perceived Stress Scale [44,45], Revised Stigma Scale (RSS) [46,47], Korean version of the Neurological Disorders Depression Inventory for Epilepsy (K-NDDI-E) [48], Generalized Anxiety Disorder-7 (GAD-7) [49], and short forms on

Table 1
Summary of studies involving the relationship between stress and epilepsy in order that they appear in the article.

References (1st Author [#])	Title	Sample Size (n)	Stress measure	Causative or precipitating factor	Acute or chronic stress	Result
Privitera [16]	Characteristics of people with self-reported stress-precipitated seizures	266	Prospective survey	Precipitating	Acute and Chronic	Stress-precipitated seizures may be associated with either acute or chronic stress, and are associated with higher scores on anxiety tests. Patients frequently use stress reduction methods to self-treat and report high success rates.
Temkin [22]	Stress as a risk factor for seizures among adults with epilepsy	12	Prospective group analysis	Precipitating	Acute	There was a positive association between higher stress levels and increased seizures
Webster [23]	Seizure frequency and major life events in epilepsy	18	Prospective survey	Precipitating	Chronic	There was a positive association between life events and seizure frequency. Most of the patients who showed an association experienced partial seizures.
Neugebauer [24]	Stressful life events and seizure frequency in patients with epilepsy	46	Daily diaries	Precipitating	Acute	Events increased seizure frequency in more subjects, but was only significant with men.
Stevens [25]	Emotional activation of electroencephalogram in patients with convulsive disorders	30 epilepsy patients, 9 controls	Electroencephalogram (EEG) with stress interview	Precipitating	Acute	The majority of patients had abnormal EEG changes in response to psychological stress.
Feldman [28]	Identity of emotional triggers in epilepsy	5	Prospective video and audio recording in patients with epilepsy	Precipitating	Acute	Creation of empathetically stressful responses to presentation of audio and video tape recordings of specific problematic social interactions was sufficient to induce seizures in these patients.
Neufeld [29]	Stress and epilepsy: the Gulf War experience	100	Questionnaire	Precipitating	Acute	Epilepsy control was only weakly affected by an acute external emotional stress factor.
Swinkels [30]	Influence of an evacuation in February 1995 in the Netherlands on the seizure frequency in patients with epilepsy: A controlled study	30 evacuated patients and 30 matched control patients	Retrospective study	Precipitating	Acute	There is a relation, albeit small, between a stressful life event and seizure frequency.
Bosnjak [31]	Effect of war on the occurrence of epileptic seizures in children	72 children from war-affected and 39 children from non-war-affected areas	Retrospective chart review	Precipitating	Acute	There was a higher frequency of epileptic seizures during the war in children from war-affected areas, particularly with absence seizures.
Thapar [32]	Stress, anxiety, depression, and epilepsy: investigating the relationship between psychological factors and seizures	433	Longitudinal cohort study	Precipitating	Acute	Stress, anxiety, and depression all predicted change in seizure recency, with depression being the most influential.
Moshe [33]	Occurrence of seizures in association with work-related stress in young male army recruits	300,000	Longitudinal cohort study	Precipitating	Acute	There were increased rates of seizures in the combat unit group, possibly due to increased physical and mental stress.
Blanchet [34]	Mood change preceding epileptic seizures	27 patients with epilepsy, 13 had seizures	Questionnaire	Precipitating	Acute	Mood ratings on 8 of 10 scales declined on the day(s) preceding a seizure.
Szaflarski [35]	Functional MRI of facial emotion processing in left temporal lobe epilepsy	34 patients with left temporal lobe epilepsy (LTLE), 30 matched controls	Cross-sectional study	Precipitating	Acute	In patients with LTLE there is a significant relationship between seizure control and emotional processing.
Haut [36]	Clinical features of the pre-ictal state: Mood changes and premonitory symptoms	19	Prospective electronic diary study	Precipitating	Acute	Pre-ictal changes in mood and premonitory features may predict seizure occurrence.
Haut [37]	Seizure occurrence: precipitants and prediction	71	Prospective paper diary study	Precipitating	Acute	Lack of sleep and higher self-reported stress and anxiety levels were associated with seizure occurrence.
Christensen [38]	Stress and epilepsy: A population-based cohort study of epilepsy in parents who lost a child	94 parents who lost a child, 882 had not	Population-based follow-up study	Causative	Chronic (more than acute)	Stress was associated with a moderately increased risk of being diagnosed with epilepsy.
Gelisse [39]	Can emotional stress trigger the onset of epilepsy?	Of 4618 patients, 22 had a major life event 3 months prior to epilepsy onset	Retrospective chart review and survey study	Causative	Acute	Some patients began their seizures in the wake of significant life events and may be the cause of their epilepsy.
Allendorfer [40]	Physiologic and cortical response to acute psychosocial stress in left temporal lobe epilepsy—A pilot cross-sectional fMRI study	23 patients with LTLE, 23 matched controls	Cross-sectional study	Precipitating	Acute	A significant relationship was found between seizure control in patients with LTLE and both HPA axis and fMRI BOLD reactivity to acute psychosocial stress.
van Campen [41]	Relation between stress-precipitated seizures and the stress response in childhood epilepsy	64 children with epilepsy,	Retrospective questionnaire, prospective 6-week	Precipitating	Acute	Stress-sensitivity seizures is associated with alterations of the stress response.

Table 1 (*Continued*)

References (1st Author [#])	Title	Sample Size (n)	Stress measure	Causative or precipitating factor	Acute or chronic stress	Result
		40 matched controls	diary, and experimental stress manipulation			
Lee [42]	Childhood trauma in patients with self-reported stress-precipitated seizures	236	Prospective survey	Precipitating	Acute and Chronic	Patients with stress-triggered seizures are more likely to endorse a history of childhood traumatic experience, particularly emotional abuse.
Moon [43]	Perceived stress and its predictors in people with epilepsy	260 patients with epilepsy, 200 controls	Case-control cross-sectional study	Precipitating	Acute and Chronic	In patients with uncontrolled epilepsy, psychiatric (depression and anxiety) and sleep-related problems had the greatest impact on their perceived stress scale.

the Patient-Reported Outcomes Measurement Information System-Sleep Disturbance (PROMIS-SD) and Patient-Reported Outcomes Measurement Information System—Sleep-Related Impairment (PROMIS-SRI) scales [50,51]. A total of 260 patients and 200 controls were included. The mean score of perceived stress scale was significantly lower in patients with well-controlled epilepsy and higher in those with uncontrolled epilepsy, compared to controls. The strongest predictor for the perceived stress scale score was the depression evaluation (K-NDDI-E), followed by the PROMIS-SRI score, the anxiety scale score (GAD-7), and seizure control. Psychosomatic factors showed a direct and indirect (seizure control) effect on the perceived stress scale score. In conclusion, this article suggested that rapid detection and appropriate management of psychiatric and sleep-related problems in patients with epilepsy and perceived stress may lessen stress and possibly improve seizure control.

Different treatments have been used to attempt to target stress and reduce seizures. Interventions targeting psychological change, education, and self-management skills have been used [52–65]. A recent review article evaluated psychobehavioral therapies in improving seizure control [52]. In this article, Tang et al. summarized randomized controlled trials used to help treat epilepsy patients. The trials were placed into three main groups: behavioral approaches (relaxation, cognitive behavioral therapy), mind-body approaches (yoga), and multimodal educational interventions. This review showed that all three categories of psychobehavioral therapy consistently demonstrated positive effects on well-being. However, the effects on seizure control are inconsistent and difficult to develop clear treatment recommendations, particularly due to small clinical trial size and inadequate control groups. The authors concluded that randomized controlled trials which are blinded, have significant power, and have well-defined therapeutic components with clear objective and subjective outcome measures are still needed to draw clear therapeutic guidelines.

In a subsequent study, Tang et al., evaluated mindfulness-based therapy for epilepsy in a prospective, randomized trial [53]. Sixty patients with drug-resistant epilepsy were randomized to mindfulness-based therapy or social support. The primary outcome was quality of life and secondary outcomes were seizure frequency, mood symptoms and neurocognitive functions. Both groups improved on the primary outcome, but more patients in the mindfulness group had “clinically important improvement” in quality of life. The secondary outcomes showed significantly greater reduction in depressive and anxiety symptoms, seizure frequency, and improved delayed memory in the mindfulness group. The methodology of this study was more rigorous than prior studies and showed that mindfulness, which has been employed in many different disease states, may have great utility in seizures and common co-morbidities affecting people with epilepsy. It appears that mindfulness-based therapy may be useful even if the patient does not report stress as a seizure trigger as was reported by patients in the Privitera et al. clinic survey [16].

The large majority of studies included in this review evaluated acute stress as a precipitating factor for seizures. As detailed above, two studies evaluated stress as a causative factor, specifically the Gelisse et al. study which investigated the role of acute adverse stress as a trigger for the onset of epilepsy [39] and the Christensen et al. study which evaluated the risk of developing epilepsy in parents exposed to severe stress caused by loss of a child [38]. Furthermore, the Christensen study evaluated chronic stress, i.e. loss of a child in the past. Other studies that addressed chronic stress or both acute and chronic stress as the seizure precipitant was the Webster article evaluating seizure frequency and major life events in epilepsy [23], Privitera’s’ evaluations in 2014 and 2015 of patients who self-reported stress-precipitated seizures [16,42], and Moon’s case-control cross-sectional study evaluating perceived stress and its predictors in patients with epilepsy [43]. Differences in acute or chronic stress and stress as the precipitating or causative factor has different significance and different neurobiological underpinnings, as explored by Galtrey et al. [26]. Refer to Table 1 for a comprehensive summary of the studies included in this review.

Stress is a subjective and highly individualized state of mental or emotional strain. Although it is quite clear that stress is an important and common seizure precipitant, it remains difficult to obtain objective conclusions about a direct causal factor for epilepsy patients. Nevertheless, small prospective trials using general stress reduction methods have shown promise in improving outcomes in people with epilepsy. Large scale randomized controlled trials are needed to convince patients and providers that stress reduction methods should be standard adjunctive treatments for people with epilepsy. Finally, the data on higher anxiety levels in patients with epilepsy who report stress as a seizure precipitant mandates that any patient reporting stress as a seizure trigger should be screened for a treatable mood disorder, especially considering that mood disorders are so common in this population. Future research is needed to further clarify biological mechanisms of the stress-seizure relationship and to establish evidence based treatment recommendations.

Conflict of interest statement

Dr. Michael Privitera and Dr. Heather McKee have no conflicts of interest to disclose on this topic.

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