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Stress and Seizures

Behavioural Stress-Reduction Interventions' Efficiency in Lowering Seizure Frequency

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Abstract

Epilepsy is the most common, chronic, serious neurological disease in the world, with an estimated 65 million people affected worldwide. Recent studies on people diagnosed with epilepsy suggest that stress might trigger epileptic seizures. Interventions aimed at lowering stress might be able to reduce the risk for epileptic seizures among epileptics. In an attempt to explore this possibility, I conducted a systematic review addressing the efficacy of behavioral interventions targeted at lowering stress on seizure frequency among an epileptic population. This article also investigated the efficacy of these interventions on lowering self-perceived stress in the same population. Three databases were searched for obtaining 54 references. After a systematic filtering process, a set of 2 studies was retained after the full search procedure. The results suggest stress-reducing behavioral interventions do not have any statistically significant effects on lowering seizure frequency but have a statistically significant effect on lowering self-perceived stress ratings among an epileptic population. The small but promising results from trials and systematic reviews not included in this review warrant further research into the topic. Limitations regarding search procedure included studies and consideration for further research and reading for the presented topics are discussed.

Keywords: Epilepsy; epileptics; people with epilepsy; PWE; stress-reduction; stress-control; stress-regulation; stress management; seizure frequency; seizure reduction; systematic review.

Stress-Reduction and its Effects on Seizure Frequency

Do you think living your life with a disposition to suddenly become unconscious, unable to control your behavior, fall to the ground and convulse rigorously at any moment would have an effect on the way you live your life? This a reality for many people with epilepsy who live their daily life not fully knowing if they will experience an epileptic seizure or not that day. These individuals run the risk to be seriously injured, experience mood disorders or even lose their lives (Beghi, 2009; Harden & Goldstein, 2002). Because of the earlier mentioned factors and the risk to lose consciousness during a seizure, interest has been growing to investigate epilepsy in the hopes that understanding the mechanisms that give rise to seizures and underlie impairment of consciousness could lead to improved treatments for epilepsy and other disorders of consciousness (Blumenfeld, 2012).

For the time being the most well-established way of treating epileptic seizures is by using anti-epileptic drugs (AED) prescribed by physicians. Experts agree on the general treatment strategy of recommending monotherapy with AED as a first step if someone is diagnosed with epilepsy in the vast majority of cases. In some cases, AED is considered the only way of going by treating epileptic patients, even though about a third of patients remain resistant to AED usage (Karceski, Morrell, & Carpenter, 2001; Moshé, Perucca, Ryvlin, & Tomson, 2015). According to a survey, 50% (50 out of 100) of AED users experience bothersome side effects of seizure medications (Fisher et al., 2000). Moshé et al. (2015) mention in their article that AED treatment works successfully in the majority of cases, but have been correlated with having severe side-effects with such as depression, memory problems, obesity, and irritability. Perucca & Gilliam (2012) claim that adverse effects from AED treatment continues to be the leading cause of treatment failure and a significant determinant of impaired health-related quality of life in people with epilepsy.

Complementary treatment to AED treatment may help reduce seizure frequency among epileptic patients and not add further adverse side effects (Schachter, Shafer, & Sirven, 2013). Behavioral interventions with the aim to reduce stress might be one of the most promising complementary treatment options to study since epileptic patients frequently report stress as the most common precipitant to triggering epileptic seizures (McKee & Privitera, 2017). In this review, I will aim to summarise the existing literature on behavioral interventions aimed to reduce stress and their efficiency in lowering seizure frequency and self-perceived stress.

1. Background

1.1 Prevalence of Epilepsy

With 65 million people afflicted worldwide, epilepsy is the most common and severe neurological disease in the world. With having descriptions of epileptic seizures that date back at least to the time of Hippocrates (Thurman et al., 2011; Fisher et al., 2017). According to Thurman et al. (2011), the prevalence of active epilepsy is 5–8 per 1000 in high-income countries and 10 per 1000 population in low-income countries, with even higher rates being reported in rural areas (Moshé et al., 2015).

1.2 Risks with Epilepsy

Epilepsy is defined as a neurological disease where one has an enduring predisposition to experience epileptic seizures (Fisher et al., 2014). Epileptic seizures are defined as a brief occurrence of symbols or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. The sudden abnormal electrical disturbance can manifest in several behavior symptoms, e.g., vigorous shaking, strange movement of the limbs, becoming stiff and unresponsive (Fisher et al., 2005). I will discuss these phenomena in-depth later in this thesis and have chosen to explain them briefly to make it easier to understand the arguments and explanations to follow.

Epileptic seizures can result in several injuries. Most injuries are minor, where the most common ones include bruises and wounds, followed by abrasions, bone fractures, burns, sprains/ strains and brain concussions (Beghi, 2009). According to Forsgren et al. (2005), the risk of dying is 1.6 to 3 times higher for people with epilepsy than the general population. Where sudden unexpected death (SUDEP) is the most common disease-related cause of death for people with epilepsy. SUDEP occurs when a person with epilepsy who is in their usual state of health dies unexpectedly. The death is not related to an accident and no other cause of death can be found after an autopsy. While the mechanisms of SUDEP are unknown, it is approximated that 1 out of every 1,000 people diagnosed with epilepsy die of SUDEP each year (Moshé et al., 2015).

Patients diagnosed with epilepsy also have a higher risk of accidental death than the general population. Accidental causes of deaths include; drowning, suffocation, falls, and transport accidents (Beghi, 2009). People with epilepsy, especially those with active epilepsy, reported significantly worse psychological health, more cognitive impairment, difficulty in participating in some social activities, and reduced health-related quality of life (HRQOL) compared with a normal population without epilepsy (Kobau et al., 2014). Adults with an epilepsy history are well below national averages for the percentages of adults who report good or better mental and physical health, and they are significantly worse on positive mental and physical health functioning than

adults with different common chronic diseases such as heart disease and cancer (Kobau, Cui, & Zack, 2017). According to Gaitatzis, Trimble, & Sander (2004), epilepsy can be associated with significant psychiatric illness. With mood disorders being the most common culprit, particularly depression, followed by anxiety disorders, psychoses and personality disorders. Fiest et al. (2013) showed in their systematic review and meta-analysis that epilepsy had a statistically significant correlation with depression, with depression being deemed as being highly prevalent among epileptics according to the authors.

1.3 Treatment of Epilepsy

Karceski et al., created a consensus guideline for the treatment of epilepsy, by summarizing the expert opinion of a group of 51 physicians from different parts of the United States who specialize in epilepsy (2001). As a first step for treating the vast majority of epileptic patients, the experts recommend anti-epileptic drug (AED) monotherapy. If this fails, a second AED monotherapy should be tried. Following this, the experts are split between additional trials of AED monotherapy and a combination of two therapies, e.g. AED and vagus nerve stimulation. If the former treatment steps fail in treating the epilepsy, most experts agreed that the next step should be additional trials of two therapies, with less agreement as to the next best step after this. The experts agree to recommend an evaluation for surgery after the third failed step in-treatment of the epilepsy if the epilepsy is focal (the seizure arises in part of the brain) (Karceski et al., 2001).

1.4 Problematization

Drug treatment. The World Health Organisation (WHO) defines an adverse drug effect as "a response to a drug that is noxious and unintended and occurs at doses normally used for the prophylaxis, diagnosis or therapy of disease or for modification of physiological function" (WHO, 1972). AEDs does come with its potential risks, with common forms of AEDs having one or several adverse effects (Brodie, 2017). Perucca & Gilliam (2012) claim that it is the adverse effects of AED treatment that remain the principal cause of treatment failure and a significant determinant of impaired HRQOL in people with epilepsy. These adverse effects can develop acutely or many years after starting treatment, can affect any organ and result in early AED treatment discontinuation in up to 25% of patients.

AEDs might have side effects that can have a negative effect on lifestyle in adolescents and adults, which can also adversely influence their quality of life. According to Brodie (2017) producing or worsening psychiatric comorbidities with AEDs can cause a bigger clinical problem for the patient than epilepsy itself. The author continues by stating that there are potentially life-threatening adverse effects associated with some antiepileptic drugs, with 10 out of the 21 most

common AEDs having one or several of these potentially life-threating effects. With some of the more common potentially life-threatening adverse effects with AEDs being Stevens-Johnson syndrome, hepatotoxicity and aplastic anemia (Brodie, 2017; Perucca, & Gilliam, 2012).

Antiepileptic drugs work by producing global changes in the excitation levels in the central nervous system (CNS) by either suppressing neuronal excitability or enhancing inhibitory neurotransmission. These changes can impair neuropsychological functioning and give rise to varying cognitive and behavioral deficits. AEDs can also have a negative effect on mood and have been correlated to several mood disorders (Kwan & Brodie, 2001; Ortinski & Meador, 2004). AEDs effect on the CNS can lead to adverse effects including drowsiness, fatigue, dizziness, unsteadiness, blurred or double vision, difficulty concentrating, memory problems, irritability, and depression (Perucca & Gilliam, 2012). Depressant cognitive side effects such as sedation, somnolence, insomnia, distractibility, and dizziness are frequent in adult patients, whereas in children aggression and hyperactivity may occur (Ortinski & Meador, 2004). AEDs may also have an effect on an epilepsy patient's hormones and which may result in sexual problems, fertility difficulties, menstrual disturbances, or osteoporosis (bone disease) according to Svalheim, Sveberg, Mochol, & Taubøll (2015).

Older adults (65 and over) with epilepsy may experience greater disability then adolescents and adults because of deteriorations in health due to old age, having several co-occurring health conditions, and a higher possibility of adverse effects from seizure medications due to altered pharmacokinetics and possible interactions with other medications (Faught, 1999). These impairments can decrease their quality of life and increase the need for health services and long-term care (Guralnik, Fried, & Salive, 1996). The number of available antiepileptic drugs (AED) to use for the treatment of epilepsy has increased substantially during the past 20 years, though 3 out of 10 patients still remain resistant to AED treatment. Despite improved effectiveness of surgical procedures, with more than half of operated patients achieving long-term freedom from seizures, epilepsy surgery is still only performed in a small subset of drug-resistant patients (Moshé et al., 2015). Because of the side-effects of AED treatment epileptic patients might want to go off treatment during their lifetime. With epileptic patients being able to consider the gradual discontinuation of AED therapy after at least 2 years of seizure freedom (Moshé et al., 2015).

Absence of complementary treatment. AED treatment is the most common form of treatment, with little scientific exploration of complementary treatment to lessen the risks of epileptic seizures of patients. Little is known about the prevalence of some common health behaviors such as alcohol use, cigarette smoking, level of physical activity, and sleep patterns in

people of with epilepsy (Cui, Zack, Kobau, & Helmers, 2015). According to Cui et al., (2015) adults with epilepsy are significantly less inclined than adults without epilepsy to engage in suggested levels of physical activity and to get the optimal amount of sleep for optimal health and well-being. With only 35% of adults with active epilepsy accomplishing the recommended physical activity guidelines from the World Health Organization (WHO) of doing aerobic exercise for 150 or more minutes per week of light- to moderate-intensity activity, 75 or more minutes per week of vigorous-intensity activity, or an equivalent combination of the two. Normal adults reported significantly higher compliance to WHOs guidelines, with 61.5% accomplishing the physical activity recommendations (Marques, Sarmento, Martins, & Nunes, 2015). Physical exercise could reduce mood disorders related to epilepsy such as depression and anxiety (Arida, de Almeida, Cavalheiro, & Scorza, 2013). Unfortunately, despite these health benefits, only slightly more than one-third of doctors or other health professionals recommend physical activity to people with active epilepsy (Cui et al., 2015). In the same study by Cui et al. (2015) only 50% with active epilepsy reported sleeping the encouraged amount of sleep of 7 or 8h each day, this was significantly lower than the group of people without epilepsy, with 62% of people without epilepsy reported sleeping 7 or 8h each day.

Cui et al., (2015) concludes in their paper that promoting complementary treatment as improved sleep quality and physical activity is necessary for adults with epilepsy, and ending tobacco use and maintain low levels of alcohol consumption would also improve the health of adults with epilepsy. According to Kobau & DiIorio (2003) stress, irregular sleep and, alcohol abuse are the most common factors for an increase in seizure frequency among people with epilepsy.

The Relationship between Stress, Epilepsy, and Seizures. The experience of *stress* is a common part of daily life. According to Novakova, Harris, Ponnusamy, & Reuber (2013), stress is part of an adaptive mechanism that prepares the organism to respond appropriately to challenging or threatening stimuli. The concept of stress is usually studied from three main theoretical perspectives, being (1) the psychological perspective, focusing on the individual's subjective appraisals of events and the individuals capacity to cope with them; (2) the biologic perspective, studying the physiologic stress responses, in particular neuroendocrine and immune processes, and (3) the environmental perspective, concerned with external events that can be objectively considered as stressful; and their effects on health (Novakova et al., 2013). I will look at the possible hypothesis and theories to how experienced stress can cause seizures from a psychological

and physiological perspective since I regard these perspectives to be more within the scope of this thesis and being more within the field of cognitive neuroscience than the environmental perspective.

Physiologic stress and seizures. According to Aldwin (2007), the physiologic stress response is mediated by the neuroendocrine system, which triggers the activation and the following restoration of the organism's functions in order to adapt to a given stressor. Multiple brain regions are involved in this process, including the hypothalamus, amygdala, cingulate cortex, prefrontal cortex, septohippocampal region, and brainstem structures (Van de Kar & Blair, 1999). According to Cohen, Kessler, & Gordon (1997), the sympathetic−adrenomedullary (SAM) system and the hypothalamic−pituitary−adrenocortical (HPA) axis are the primary systems central to the regulation of the physiological stress response. With many of the neurochemicals, neural substrates, and circuits involved in the regulation of the physiological stress response also being involved in the generation of seizures (Novakova et al., 2013).

The HPA axis. According to Myslobodsky (1993), the HPA axis stress mediators have an effect on inhibitory and excitatory processes in brain regions that are commonly associated to epilepsy, making them correlated to both the incitement and suppression of seizure activity. The HPA hormones corticotropin−releasing hormone (CRH) and the corticosteroid hormones are hypothesized to play a role in increasing seizure risk during stressful events (Joëls, 2009; Lai & Trimble, 1997). Experimental studies on mice with repeated administration of the above mentioned HPA hormones, and the exposure to stressful inducing interventions, e.g., foot shock, social intrusion and tail suspension, has shown to significantly increase the frequency and duration of epileptic-like EEG activity (Castro et al., 2012; Forcelli, Orefice, & Heinrichs, 2007; Schridde, & van Luijtelaar, 2004; Tolmacheva, Oitzl, & van Luijtelaar, 2012). According to Novakova et al. (2013), these experimental studies suggest that stress can be regarded as a seizure trigger but because the replication of the experiments have shown inconsistent results the author suggest that there are not enough replicated studies to draw the conclusion that the activation of the HPA axis and its secretion of CRH and the corticosteroid hormones definitively leads to seizures.

SAM system. The sympathetic−adrenomedullary (SAM) system is the other primary system central to the regulation of the physiological stress response (Cohen et al., 1997). The SAM system responds to stress via the autonomic nervous system (ANS), consisting of the sympathetic and parasympathetic nervous systems (SNS and PNS). The PNS and SNS regulate our homeostatic state (internal physiological equilibrium) by a mutual antagonistic interplay on our internal organs (Porges, 1992). To potential stressors, PNS activity is suppressed and SNS increased, this can be

seen when a stressor is appraised as to be potentially threating thus activating the "fight-or-flight response" by suppressing PNS and increasing SNS. When exposed to a stressful stimulus the hypothalamus releases hormones that incite the adrenal medulla to secrete adrenaline and noradrenaline, which then causes arousal and prepares the organism for appropriate action (Aldwin, 2007). Epileptic electrical activity often affects parts of the brain involved in regulating the tone of the ANS which can then be associated with changes in SNS and PNS tone. Changes in SNS and PNS tone can, in turn, be detected by analyzing heart rate variability (HRV) (Sevcencu & Struijk, 2010)

Possible evidence for a link between stress and epileptic seizures is provided in a study by Jeppesen, Beniczky, Fuglsang-Frederiksen, Sidenius, & Jasemian (2010). In the study, PNS activity was measured by analyzing HRV patterns, and it was shown that PNS activity was suppressed for 10s prior to epileptic seizure onset, detected by EEG. A similar finding of suppressed PNS was detected over 30s before seizure onset in epileptic patients (Novak, Reeves, Novak, Low, & Sharbrough, 1999). A suppressed PNS and elevated SNS tone have been found in people with epilepsy in between seizures in their normal life when analyzing HRV (Ponnusamy, Marques, & Reuber, 2011). This might indicate that people with epilepsy might be under chronic arousal and explain why epileptic patients are so inclined to perceive life as more stressful and interpret their seizures being triggered by experienced stress (Privitera et al., 2014). Although, there is conflicting research, with a study by Persson, Ericson, & Tomson (2007) showing no differences in autonomic nervous system activity between newly diagnosed patients with epilepsy and healthy controls when analyzing HRV. Although the research points to the existence of a possible stress-response pattern of increased SNS and suppressed PNS tone preceding the onset of seizures and being a possible link for how stress can cause seizures (Novakova et al., 2013), the evidence on the matter is limited and needs further investigation.

Psychological stress and seizures. Psychological models of stress emphasize the role of the subjective interpretation of a stimulus or event (Lazarus & Folkman, 1984). People with epilepsy report significantly higher levels of psychological distress than healthy controls and persons with a history of asthma, high cholesterol, high blood pressure, and cancer (Moore, Elliott, Lu, Klatte, & Charyton, 2009). Stress is the most self-reported trigger for epileptic seizures by people with epilepsy (McKee & Privitera, 2017; Novakova et al., 2013; Privitera et al., 2014). One hypothesis for the relationship between high reported stress and seizures are the disabling effects of living with epilepsy and experience recurrent seizures, each being an acutely stressful event, which may cause the stress that epileptic patients are inclined to report being high (Ponnusamy, Marques, & Reuber,

2012). These studies, however, are all retrospective self−report studies where participants had been asked what was the precipitating event before the seizure in retrospect, which raises the possibility that the participants might have reported a biased answer or inaccurately. A study by Pinikahana & Dono (2009) concluded that 87% of patients reported being aware of experiencing symptoms, e.g., anxiety and confusion, before having a seizure, but only 64% claimed they could tell when a seizure is about to occur. The retrospective design used in most psychological studies of stress and seizures coupled with the absence of a precise definition and a standardized, validated assessment of self−perceived stress (Novakova et al., 2013) makes drawing a causal link between stress and seizure hard to do.

A good option to retrospective designed studies on the relationship between stress and seizures might be prospective design studies. Prospective studies have however contributed less distinct evidence for the correlation between stress and seizures compared to retrospective studies. Self-reported high stress among people diagnosed with epilepsy was the best predictor of seizures in the next 24-hours in a study by Haut, Hall, Masur, & Lipton (2007). The study, however, had several limitations being stress was not assessed using a standardized scale, stress-levels were only reported once a day, and the study used paper diaries which made it possible for participants to record stress levels retrospectively, possibly introducing bias (Litt & Krieger, 2007).

Stress is the most self-reported trigger for epileptic seizures by people with epilepsy, however, the evidence for the causal role of how stress triggers epileptic seizures is still inconclusive (Haut & Privitera, 2019). Even though the evidence for the causal relationship between stress and seizures is inconclusive and sometimes contradictory, stress is currently accepted as a possible risk factor for triggering seizures in the field of epilepsy (Novakova et al., 2013; Tang, Michaelis, & Kwan, 2014).

Privitera et al. (2014) found in their survey of 219 epileptic patients that 57% of patients that reported stress as a precipitant to triggering epileptic seizures had tried a stress-reduction intervention, with 88% out of this group saying it lowered seizure frequency. Among the patients that reported stress not being a precipitant to seizures, 25% had tried relaxation or stress-reduction, and 71% of this group thought it lessened seizure frequency. A hypothesis to how stress-reduction interventions may prevent the build-up of seizure activity is that stress may alter autonomic nervous system functioning by increasing SNS activity, stress-reduction interventions are thereby possibly effective by increasing the antagonistic PNS response to restore homeostasis. Restoring the equilibrium within the autonomic nervous system in this way, can hence, create beneficial effects

for patients with epilepsy by reducing the physiological stress-response which then might be perceived by the patient and give rise to lower perceived stress-scores (Tang et al., 2014).

Stress-reduction interventions. There are several approaches within stress-reduction designed to alleviate stress, e.g., behavioral approaches, cognitive-behavioral approaches, and mind-body approaches (Tang et al., 2014). With mind-body interventions perhaps being the easiest approach for the average epileptics to start with today as complementary, e.g., starting a course in yoga might prove to be easier to start with then, e.g., a cognitive-behavioral approach without education in cognitive behavioral therapy (CBT). With CBT treatment for epileptics, one might try to influence the individual's perception of their health locus of control, use cognitive restructuring techniques and goal setting exercises (Tang et al., 2014). If interested in exploring CBT interventions effect on seizure frequency the reader is referred to "Taking control of your epilepsy: a workbook for patients and professionals" (Reiter, Andrews, & Janis, 1987).

Behavioral stress-reduction interventions, e.g., relaxation training, mindfulness meditation, and yoga exercises have demonstrated promising results in lowering seizure occurrence in patients with epilepsy in small trials. The results have however been small and inconsistent (McKee & Privitera, 2017; Tang et al., 2014). I aim to rectify this issue with this systematic review and explore if behavioral stress-reduction interventions are a viable option as a complementary treatment for people with epilepsy to reduce seizure frequency and lower self-perceived stress.

1.5 Research Aims

In this review, I will not search for any stress-reduction approach in particular, instead, I will do a broad search for articles the authors themselves have labeled the intervention as being stress reducing in nature. I aim at summarizing the present literature on behavioral stress-reduction interventions efficiency in lowering seizure frequency and self-perceived stress among clinically diagnosed epileptics, with or without AED usage, and exclude studies where age-dependent epilepsy syndromes among participants are present. Since information on the topic is scarce I will be lenient with the year of publication. I will look specifically at articles that mention stress-reduction or similar terminology and measures seizure frequency and self-perceived stress. The possible implications of this systematic review are finding stress-reduction interventions that could significantly decrease seizure frequency among epileptic patients, which could be added to traditional AED treatment without adding adverse side effects. Regarding the participants, I will only use articles where the mean age is between 18-65 years old. This is to lessen the risks of including age-related epilepsy syndromes that are more common for people under 18 and over 65. The search will include both females and males. There must be a comparison group present in the

studies, e.g., in the form of a control or placebo group. Papers on stress-reduction interventions often include self-report measurements to try and measure the subjects own experience of stress and seizures (Tang et al., 2014). Since the high availability of self-report measurements used in stress-reduction studies and my interest in the psychological perspective and the frequency of patients self-reporting stress as a precipitant to triggering epileptic seizures, I will use self-report assessments as the primary assessment method for my results. Main outcomes are seizure frequency and self-perceived stress.

1.6 Key Concepts, Definitions, and History of the Literature

Epilepsy. Fisher et al., (2005) released a conceptual definition of seizures and epilepsy, followed by an operational (practical) definition in 2014 (Fisher et al., 2014) that is more fit for the purpose of clinical use. This paper will focus on the operational (practical) definition from 2014 (Fisher et al., 2014) since I am interested in using a clear definition to check so that all participants have been clinically diagnosed the same way. According to Fisher et al. (2014, p. 475-482) "epilepsy is a *disease* characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition". One can be diagnosed with epilepsy after having two *unprovoked* (or reflex) seizures more than 24 hours apart or having one unprovoked seizure when the risk for another seizure is known to be high (>60%).

The International Bureau for Epilepsy (IBE) and the International League Against Epilepsy (ILAE) recently agreed that epilepsy should be considered a *disease*. Epilepsy has traditionally been regarded as a disorder or a family of disorders, rather than a disease, to highlight that it is composed of many different illnesses and conditions. *Disease* in this context may convey a more lasting derangement of normal brain function then disorder. Fisher et al. (2014) suggest that the term disorder is poorly understood by the public and minimizes the serious nature of epilepsy.

A seizure that is stimulated by a temporary factor acting on an otherwise normal brain to briefly lower the seizure threshold does not count toward a diagnosis of epilepsy. A seizure after a fever, concussion, or in association with alcohol−withdrawal, each would exemplify a stimulated seizure that would not result in a diagnosis of epilepsy. While a brain tumor that might cause a person to have an epileptic seizure, would for example, not be seen as a transient factor. The term *unprovoked* signifies the absence of a transient or reversible factor momentarily lowering the threshold and producing a seizure at that point in time (Fisher et al., 2014). Epilepsy can be deemed as *resolved* if a person has been seizure−free for the last 10 years, with at least the last five years

being without AED treatment, or when that person has passed the age of an age−dependent epilepsy syndrome. When epilepsy is considered *resolved,* it indicates that the person no longer has epilepsy, although this does not assure that it will not return (Fisher et al., 2014).

According to Berg et al. (2010), there are three categories one can use to describe the causes of epilepsy. Being: *Genetic, Structural/metabolic, and Unkown cause*. *Genetic epilepsy:* The diagnosed epilepsy is, as best understood, the direct result of a known or presumed genetic defect(s) in this case, in which seizures are the core symptom of the disease. However, this does not exclude the environmental factors (outside the individual) may contribute to the expression of disorder (Berg et al., 2010). *Structural/metabolic:* There is a clear structural or metabolic condition or disease that has been demonstrated to increase the risk of developing epilepsy considerably. These disorders may be of acquired or genetic origin. Acquired disorders being, e.g., stroke, trauma, and infection. Those of genetic origin being, e.g., tuberous sclerosis, and, many malformations of cortical development. When the disorder is of genetic origin, there is a separate disorder interposed between the gene defect and epilepsy (Berg et al., 2010). *Unknown*: The characteristics of the underlying cause is unknown; it may have a fundamental genetic basis or it may be the consequence of an unrecognized metabolic or structural disorder not yet identified (Berg et al., 2010).

Epileptogenesis is defined as the process whereby a neuronal network develops recurrent epileptic seizures anew or following an insult. One can develop epilepsy during any time in one's life span, but the risk for seizure occurrences is at its peak in infancy and childhood during the human lifespan. Epileptogenesis results from a temporal progression of cascading molecular and cellular changes that lead to network reorganization (Rakhade & Jensen, 2009). Aside from the inherited forms of epilepsy and epileptogenic malformations of cortical development, most cases of earlylife seizures are associated with external insults such as fever, trauma or hypoxic-ischemic encephalopathy (impaired cerebral blood flow and oxygen delivery to the brain) (Vannucci, 2000). These external insults can lead to the development of epilepsy in later life. Epilepsy can also develop following a variety of brain insults, e.g., brain tumors and infections of the brain, but the development of epilepsy after traumatic brain injury (TBI) or stroke are the best-characterized examples of epileptogenesis in adults. The onset of epilepsy can be delayed following the initial insult and can take 5 years or more to emerge after traumatic brain injury (Rakhade & Jensen, 2009).

Seizures. There have been descriptions of seizures that date back at least to the time of Hippocrates (Fisher et al., 2017) but is not until recently there has been international agreement on the definition of the term seizure. The ILAE and the IBE defined an epileptic seizure as a transitory

event of signs and/or symptoms due to *abnormal excessive* or *synchronous neuronal activity* in the brain (Fisher et al., 2005). *Abnormal excessive neuronal activity* refers to uncommon responsiveness (e.g., lower threshold) of a neuron to excitatory input, making it hyperexcitable. This, in turn, makes the neuron prone to fire bursts of multiple action potentials instead of just one or two. *Synchronous neuronal activity* refers to the recruitment of large numbers of neighboring neurons into an uncommon firing mode. At its core, a seizure is a network phenomenon that requires the participation of many neurons firing synchronously (Rho, Sankar, & Stafstrom, 2010). Fisher et al. (2005) define an epileptic seizure as a clinical event and make the argument that signs and symptoms of a seizure must be featured prominently in the definition. However, detailed specification of subjective and objective clinical phenomena during an epileptic seizure is difficult, because of the wide range of possible manifestations. Seizure manifestation depends on the location of onset in the brain, sleep-wake cycle, maturity of the brain, medications, and a variety of other factors. Seizures can affect motor, sensory, and autonomic function; consciousness; emotional state; cognition; memory; or behavior, seizures do not affect all these factors but all influence at least one (Fisher et al., 2005). It is the cerebral cortex that is the primary element in the generation of epileptic seizures, but it is not the only one. Epileptic seizures can also originate in the limbic system, thalamocortical interactive systems or in the brainstem (Fisher et al., 2005).

Classification of seizure types. The starting point of the Epilepsy classification structure is to determine the seizure type (Scheffer et al., 2017). The seizure type classification begins with the determination of whether the initial manifestations of the seizure are of focal, generalized or unknown origin. *Focal*: In 2017 Fisher et al. conceptualized focal epileptic seizures as originating within neural networks limited to one hemisphere. These focal seizures may originate in subcortical structures and not only in cortical structures. They may be discretely localized or more widely distributed. A seizure arising from the right motor cortex, for example, may cause jerking movements of the left upper extremities. *Generalized*: In contrast, generalized epileptic seizures are conceptualized as originating at some point within, and rapidly engaging bilaterally distributed neural networks. Such bilateral networks can include cortical and subcortical structures, but do not necessarily include the entire cortex. An example would be generalized tonic-clonic seizure types, which is the seizure type most often portrayed in media and the one people most often picture when they try to describe an epileptic seizure, where the person might lose consciousness, suddenly collapse and start convulsing. Unknown: The onset of the seizure may be missed or obscured, in which case the seizure is classified as of unknown onset (Fisher et al., 2017). After classifying seizure type one tries to classify which epilepsy syndrome a person might have. An epilepsy

syndrome is a complex of signs and symptoms that define a unique epilepsy condition, e.g., Late-onset childhood occipital epilepsy (Engel, J., 2001). In this paper, I will not focus on any seizure type or epilepsy syndrome in particular, but it might be relevant to address if there is a particular seizure type or epilepsy syndrome that respond well to stress-reduction interventions after the full search procedure.

What happens during a seizure. Scharfman (2007) states that seizures can be caused by multiple mechanisms, and often they appear so diverse that one would suspect that no common theme applies. Although different mechanisms underlie focal and generalized seizures, a common way of thinking is that seizures occur when there is a disruption of mechanisms that normally create a balance between excitation and inhibition in the nervous system. There are controls that inhibit neurons from excessive action potential discharge, but there are also mechanisms that encourage neuronal firing so the nervous system can function appropriately. Disrupting these mechanisms and causing an imbalance between exciting and inhibiting activity can lead to seizures (Fisher et al., 2005; Scharfman, 2007). Although this way of thinking may be overly simplistic when brain microcircuitry is analyzed in detail (Rho et al., 2010; Scharfman, 2007).

An epileptic seizure can be separated into the pre-ictal, ictal and post-ictal phases. *Ictal* referring to the actual expression of a seizure happening here and now, and pre- and post- being temporal definitions in relation to the seizure (Mula & Monaco, 2011). These phases of the seizure can then be investigated from many different levels within brain function, e.g., neuronal networks, neuronal structures, neurotransmission, and their receptors; or ionic channels. The mechanics on all these levels can differentiate for focal or generalized seizures, and also differentiate between seizure types within the category, e.g., generalized absence seizures and generalized convulsive seizures have different mechanics on a neuronal networks level, which makes it difficult to find a common theme for all epileptic seizures (Scharfman, 2007). For the sake of my scope in this thesis and interest in investigating stress-reduction interventions effect on seizures, we will mainly investigate the ictal-phase in this review from the level of neurotransmission and neuronal networks to explore the neurological mechanisms that underlie seizures and that might be affected by stress-reduction interventions. These neurological mechanics can be potentially useful to explain the results of my systematic search in the discussion part. I choose to explore seizures from the level of neurotransmission and neuronal networks because I find them to be the most explored levels in the literature on *ictogenesis* (the generation of a seizure).

Neurotransmission. There are two basic types of neurons, depending on the neurotransmitter released from its terminals: excitatory or inhibitory. When the neurotransmitter is

sent from the presynaptic terminal, across the synaptic cleft of one neuron to the next, it binds to the specific receptor on the postsynaptic membrane (Rho et al., 2010; Stafstrom, 1998). This binding then results in a change of motion of the flow of ions (particles with either positive or negative charge) through the receptor, which then change the excitability of the postsynaptic terminal. This change in excitability results in *depolarization* or *hyperpolarization*, that is, movement of the membrane potential is taken closer or further away from the threshold voltage for the generation of an action potential (Rho et al., 2010; Stafstrom, 1998).

Inhibitory synaptic transmission. GABA is the main inhibitory neurotransmitter in the mammalian central nervous system. GABA binds to at least 2 receptors being GABAa and GABAb which is found almost all cortical neurons. The GABAa receptor is the one of greater interest in relation to being a component of epileptic firing. This is the case since activating the GABAa receptor with GABA, can results in the influx of chloride ions (Cl-) into the neuron. This Cl- influx increases the negative charge inside the postsynaptic terminal, thereby hyperpolarizing it, which then inhibits cell discharge. This change in membrane potential is called an inhibitory postsynaptic potential (IPSP). IPSP, simply put, reduces the likelihood of the neuron firing by temporarily changing the movement of the membrane potential further away from the threshold voltage for the generation of an action potential (Rho et al., 2010; Stafstrom, 1998).

Excitatory synaptic transmission. Glutamate is the principal excitatory neurotransmitter of the mammalian central nervous system. Glutamate can bind to two classes of glutamate receptors: ionotropic and metabotropic. Where the iontropic class is the class of more importance in the generation of epileptic firing (Stafstrom, 1998) and will be the one we will look into. The Ionotropic glutamate receptors are broadly divided into *N*-methyl-d-aspartate (NMDA) and non-NMDA receptors. If glutamate binds to a non-NMDA receptor this causes an influx of sodium ions (NA+) into the postsynaptic terminal, which then positively charges the postsynaptic neuron. This initiates depolarization and produces a fast-rising and brief in duration excitatory postsynaptic potential (EPSP, opposite to IPSP) which can result in an action potential discharge if the action potential threshold is reached (Rho et al., 2010; Stafstrom, 1998). To activate the NMDA receptor, the following must occur: 1) glutamate must bind to the NMDA receptor; 2) glycine, an essential co-agonist, must bind at another, nearby site on the NMDA receptor complex; and 3) magnesium ion (Mg++) blocking of the channel pore must be relieved. If the NMDA receptor is activated, it starts an influx of calcium (Ca++) and NA+ into the postsynaptic terminal, depolarizing it, and giving rise to EPSPs that are slower and longer-lasting than the ones following activation of the Non-NMDA receptor. As stated earlier, initial “fast” depolarization is mediated by non-NMDA glutamate

receptors, while sustained depolarization is a consequence of NMDA receptor activation. And it is the activation of these NMDA receptors that might cause several action potentials to fire and are the ones linked to contributing to epileptic-like burst discharge seen in epilepsy (Rho et al., 2010; Stafstrom, 1998).

Neuronal networks. As stated before in the definition of a seizure, a high amount of synchronous neuronal activity (hypersynchrony) is one of the hallmarks of a seizure. At its core, a seizure is a network phenomenon that requires the participation of many neurons firing synchronously (Rho et al., 2010). It is this concept of hypersynchrony that we will look at next. In a normal brain, an action potential fires if the cell membrane is depolarized to the action potential threshold. If a neuron fires (neuron 1) it can have an effect on the activity on a neighboring neuron (neuron 2) through electrical field (i.e., ephaptic) or synaptic mechanisms (Rho et al., 2010). This, in turn, can result in an EPSP in neuron 2. The discharge of neuron 1 activation may also activate an inhibitory interneuron (neuron 3) giving rise to an IPSP. The activation of inhibitory neuron 3 may prevent neuron 2 from generating an action potential, by means of the created IPSP to counter the depolarization caused by the EPSP (Rho et al., 2010; Stafstrom, 1998). In this way, we can envision the “tug of war” in a brain between IPSP and EPSP and how inhibition modifies ongoing excitation. If this course of events is extended to thousands of interconnected neurons, each influencing the activity of its neighbors, it is possible to see how a decrease in inhibition or increase in excitation in the neural system could lead to hypersynchronous epileptic firing in a large area of the brain. In summary, the generation of seizures is possible if the neural system is changed in such a way that it favors excitation over inhibition. In the hyperexcitable epileptic brain, this abnormal change of the neural system is constant. This chronic hyperexcitability can arise from many of the mechanisms we have gone through, but the vast majority of them either reducing inhibition, e.g., due to impaired GABA production. Or, increasing excitation, e.g., due to overactive NMDA receptors (Rho et al., 2010; Stafstrom, 1998).

Symptoms. According to Englander, Cifu, Diaz-Arrastia, & Center (2014) during a seizure the sudden abnormal electrical disturbance in the brain that can result in one or more of the following symptoms: Strange movement of one's head, body, arms, legs, or eyes, such as stiffening or shaking. The person having an epileptic seizure showing clear signs of unresponsiveness, staring, chewing, lip smacking, or fumbling movements. The person might also experience strange smells, sound, feeling, taste, or visual images. Have an experience of sudden tiredness or dizziness. And not being able to speak or understand others.

An epileptic seizure may impair a person level of awareness of themselves or the environment but that is not always the case, for instance, a person might still experience a degree of awareness even if the persons become immobile and unresponsive during a seizure. With different seizure types being able to give rise to different lengths and levels of impairment of awareness. During brief absence seizures where the person become immobile and unresponsive for a brief time, awareness and responsiveness can be at least partially retained. While during general tonic-clonic seizures a person experiences a full loss of consciousness for about 3-5 minutes (Fisher et al., 2017).

Stress-reduction interventions. There are several different behavioral interventions that we might encounter when performing our search procedure. All of them are aimed at reducing stress and may be employed as a complementary treatment with other psychobehavioral treatments for epilepsy (Tang et al., 2014). These interventions are designed to achieve a state of calmness and minimize physiological reactions to stress, with the exception being physical exercising that is designed to elevate physical stress during the activity. Examples of these are relaxation exercises, such as Jacobson's progressive muscular relaxation (PMR) and yoga exercise. Breathing techniques, such as diaphragmatic breathing, utilize awareness of breathing rate, rhythm and are often used jointly with the formerly mentioned relaxation exercises (Tang et al., 2014). Mindfulness-Based Stress Reduction has become one of the most common interventions being used by people with epilepsy in recent years. The therapeutic component of mindfulness is to acquire attention control by focusing on internal processes (breath, bodily sensations, thoughts, and emotions) and external stimuli (sights, sounds, smells, and textile) at the present moment (“here-and-now”), with nonelaborative attitude and nonjudgmental acceptance. Various skills are cultivated by being mindful; basic skills include mindful breathing, mindful eating, mindful awareness on sensations, and thought and emotional labeling (Tang et al., 2014).

Stress-reduction interventions are not necessarily aimed at curing epilepsy. Instead, they aim at assisting individuals to increase their ability to cope with their disease on a psychological level with possible underlying neurobiological alterations that might contribute to improved seizure control and psychological well-being (Tang et al., 2014).

Complementary treatment. Stress-reduction interventions have been explained to being a *complementary treatment* to AEDs during my literature search, but what does that mean? Complementary treatment is the use of treatments that works in conjunction with conventional medicine. With alternative treatments being used instead of conventional medicine. Many complementary and alternative therapies have not been studied using a strong scientific approach.

And there is lacking evidence for how they work, how useful they are or for whom they may work. The ketogenic diet (a diet very high in fat and very low in carbohydrates) began as an alternative therapy but has been scientifically tested and is now considered a conventional therapy for certain types of epilepsy syndromes (Schachter et al., 2013).

2. Method

Research question. What effects do behavioral stress-reduction interventions have on seizure frequency, and self-perceived stress in an epileptic population. With the following being the main concepts I want to search for when looking for articles: 1: Stress-reduction. 2: Seizure frequency. 3: Epileptic population.

2.1 Search Procedure

The databases Web Of Science, PubMed, and Scopus were searched in April 2019, using the following search terms: [(“stress-reduction” OR “stress management” OR “stress relief” OR “stress control” OR “stress treatment” OR “stress regulation” OR “stress therapy” OR “stress-based” OR “arousal-based”) AND (seizure* OR seizure frequency* OR seizure reduction OR seizure occurrence OR seizure prevalence OR seizure recurrence OR seizure regularity OR seizure management) AND (epileptic* OR epilepsy OR epileptic population OR “patients with epilepsy” OR “PWE”)] The search was performed with the above-mentioned terms. The search included articles that had the above-mentioned terms in the title, abstract or keywords. The search was limited to articles that were published in English and published at any time. A total result of 54 was obtained, with 20 results being found on Web of Science, 4 results on Scopus, 30 results on PubMed. I then conducted a systematic filtering process (see Fig.1). First, I removed reviews that had been included in the PubMed search. Their search function for article type to only show classical articles or clinical trials gave 0 results, so I opted to include all journal articles, where reviews were included as well. 12 of the 30 results from PubMed were reviews, leaving me with 18 articles from PubMed after exclusion. Thereafter, I eliminated 18 duplicates. Thereafter, inclusion criteria C1 to C8 (see Selection criteria below) was applied to the remaining 24 articles while screening title and abstract of the remaining papers. 4 Papers not clearly violating at least one criterion were retained for full-text examination. A set of 2 studies was retained after the full search procedure.

2.2 Selection Criteria

Studies needed to satisfy all the following criteria to be included in this review:

C1: Conducted on human subjects.

C2: The population in the study were defined as epileptic by the operational definition by Fisher et al., (2014) or had been diagnosed by a physician.

C3: Includes a self-report measurement of seizure frequency before and after the intervention.

C4: Includes a self-report measurement of stress before and after the intervention.

C5: The article is published in a peer-review Journal.

C6: Descriptions of experimental design, statistical analyses, and results of the study are complete and clearly described.

C7: The article is a peer-reviewed research report. Narrative and systematic reviews, doctoral dissertations, posters, registered study protocols, commentaries, books and book chapters, essays and other theoretical accounts were therefore excluded.

C8: The intervention is of a behavioral nature - interventions designed to affect the actions that individuals take with regard to their health - with the individual itself being able to perform the intervention and do a lifestyle change, e.g., eating well and exercising (Cutler, 2004).

2.3 Data extraction

Borderline case. I found a total of two studies to use after my full search procedure, with one of the studies being a borderline case since it broke my criterion of the population in the study all being defined as epileptic by the operational definition by Fisher et al., (2014) or had been diagnosed by a physician. In the study by Novakova, Harris, Rawlings, & Reuber (2019) they recruited a mixed group of participants with 57 patients (80.3%) being diagnosed with a form of epilepsy, and a total of 12 patients (16.9%) participants being diagnosed with the seizure disorder psychogenic nonepileptic seizures. Psychogenic nonepileptic seizures (PNES) are operationally defined as episodes of altered sensation, movement or experience similar to that of epilepsy, but caused by a psychological process and not associated with abnormal electrical discharges in the brain as in epilepsy (Reuber, & Elger, 2003). I choose to include this study despite it broke one of my criterions since the authors mention that because of the low numbers of patients with PNES, it

was not possible to perform meaningful subgroup comparisons of the two patient groups. I also choose to include the study despite breaking one of the criterions because of the very low amount of included studies after my search procedure, and my hypothesis that both groups should still show similar effects of the intervention.

I extracted the following information from each of the included studies: mean age of the sample being tested, sample size, duration of the intervention provided, total approximate dosage (in minutes), population assessed (epileptic or healthy), year of publication, name of the intervention, control group, active control (see Table 1). I then presented the main findings and important assessments used to measure seizure frequency and self-perceived stress in each included article (see Table 2). The studies included several other assessments, e.g., The Beck Depression Inventory–II, Self-Efficacy Scale and Neurological Disorders Depression Inventory for Epilepsy. I choose to focus solely on assessments regarding self-perceived stress and self-reported amount of seizures.

Figure 1. PRISMA Flowchart of Search Procedure. *Adapted from:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097.

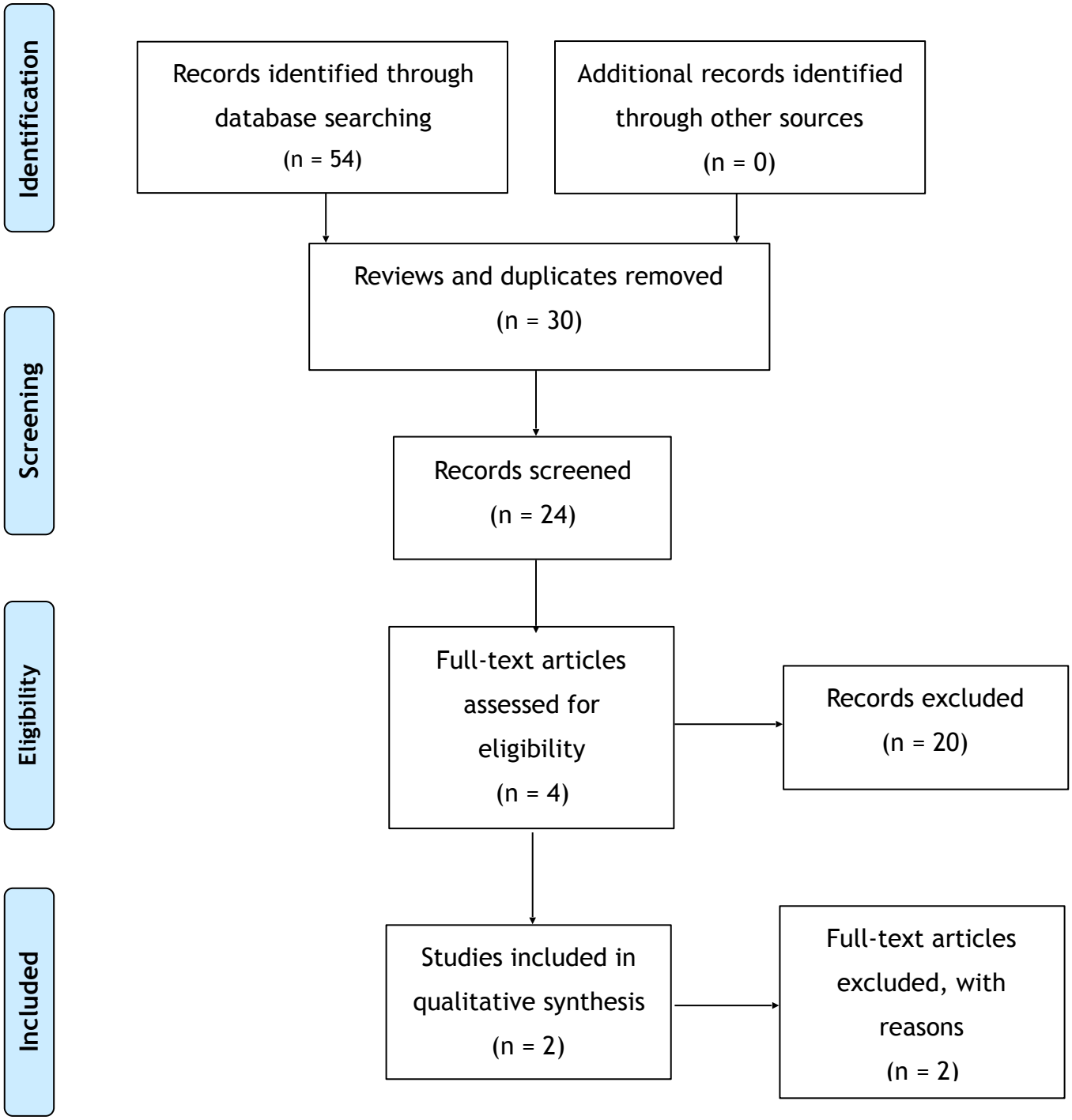

Table 1 & 2.

Table 1

Characteristics of included studies

Study	Mean age	Sample size*	Duration of intervention	Total dosage (minutes)	Population	Intervention	Control group	Active control
Haut et al. (2018)	37.2	64	2 x 15-5min daily home practice, for 12 weeks	1680	Epileptic	PMR	FA	Yes
Novakova et al. (2019)	41.87	71	Not Specified	Not Specified	Epileptic	SHSMB	1-month Delayed Intervention Group	No

Intervention: SHSMB = PMR = Progressive Muscle Relaxation; FA = Focused Attention; Self-Help Stress Management Workbook.

* Participants included in analyses, i.e., without drop-outs.

Table 2

Assessments used and main findings across included studies

Study	Assessment		Main findings
	SF	SPS	
Haut et al. (2018)	ED	ED	Both the experimental group (PMR), and the active control group (FA) showed a reduction in seizure frequency compared to baseline. They did not differ in seizure reduction. PMR was more effective than FA in reducing self-reported stress.
Novakova et al. (2019)	LSSS-3	SSSI	A significant reduction in self-reported stress ($P = .01$) with a medium effect size ($d_z = 0.51$) was observed one-month postintervention. There were no significant changes in any other measures.

SF = Seizure Frequency; SPS = Self Perceived Stress.

SF: ED = Electronic Diary; Liverpool Seizure Severity Scale = LSSS-3.

SPS: ED = Electronic Diary; Smith Stress Symptom Inventory = SSSI.

Main findings: PMR = Progressive Muscle Relaxation; FA = Focused Attention.

2.4 Measurements and Definitions in the Studies

Novakova et al. (2019) used the Liverpool Seizure Severity Scale (LSSS-3) to measure seizure frequency and the Smith Stress Symptom Inventory (SSSI) to measure self-perceived stress in the subjects. The Liverpool Seizure Severity Scale (LSSS-3) is a 12-item inventory designed to quantify the severity of a patient's seizures. Scores ranged from 0 to 100, with a higher score reflecting more significant symptoms. It provides a single-unit weighted scale that measures the severity of the most severe seizures that the patient has experienced during the past four weeks.

Reliability and validity of the scale have been demonstrated (Scott-Lennox, Bryant-Comstock, Lennox, & Baker, 2001).

The Smith Stress Symptom Inventory is a 35-item measure of stress symptoms using a four-point scale over the past month, comprising symptom categories including worry/negative emotion, attentional deficits, striated muscle tension, autonomic arousal, depression, and interpersonal conflict. Scores were averaged giving a possible score of 1–4; a higher score indicating greater stress symptomatology. Internal consistency reliability ranges from 0.76 to 0.89; validity has also been demonstrated (Novakova et al., 2019).

In the other study included in this systematic review, Haut et al. (2018) gave out smartphones as electronic diaries where the subjects made daily self-reported mood and stress ratings and also reported the daily amount of seizures. E-Diary questionnaires were administered at set intervals twice a day interval contingent (AM and PM), experience-based (one daily random entry), and event contingent (postpractice, and seizure reporting). Adherence to diary entries was high: 85.4% of AM and 82.5% of PM diary entries were completed in total. In each entry, participants completed multiple mood items adapted from the circumplex models of emotion/affect using visual analog scales (links: http://bit.do/eQhyv). Participants who missed 3 consecutive days twice or 5 consecutive days exited the study. None of the included studies in this systematic review presented a clear definition of what a seizure is. Only one of the studies presented a clear definition of stress in their study, being:

> The overall framework for the structure of the intervention was based on the integrative model of stress, according to which the experience of 'stress' comprises interactions between environmental demands; appraisal of demands and adaptive capacities; the resulting perceived stress; and the associated emotional, cognitive, behavioral, and physiological stress responses. (Novakova et al., pp. 170., 2019)

Overall, despite the variability in measurements of stress and seizure frequency, there were consistencies in the questions in the questionnaires used, and all used a self-report method to asses the amount of stress and seizures the participants were experiencing at baseline, during the intervention and post-intervention.

3. Results

Participants: The present systematic review included 2 studies sampling a total of 135 participants. Participants were recruited from epilepsy centers and neurology clinics in the USA or the United Kingdom in all studies. Sample sizes of studies ranged between 64 and 71 participants (*Msample size* = 67.5, *SD* = 3.5). These samples consisted of relatively older participants (*M* = 39.535 years, *SD* = 2.335). Haut et al. (2018) had a minimum age of participants being 18 years old

or older in their study. Novakova et al. (2019) did not specify a minimum age in their study. They referred to all recruited participants being "adult patients" (Novakova et al., pp. 170, 2019). Most participants were female (67%) when combining the grand total of all participants in all studies. 17.06 years (*SD* 15.6 years) were the mean duration of having been diagnosed with a seizure disorder in the study by Novakova et al. (2019), and 26 years (*SD* 13.7 years) being the mean of being diagnosed with epilepsy in the study by Haut et al. (2018).

In one study of the total 2 studies selected for this systematic review, all participants recruited had been diagnosed with medication-resistant focal epilepsy by a physician (Haut et al., 2018). In the study by Novakova et al. (2019) they recruited a mixed group of participants with 57 patients (80.3%) being diagnosed with a form of epilepsy, and a total of 12 patients (16.9%) participants being diagnosed with the seizure disorder psychogenic nonepileptic seizures. All studies evaluated the effects of interventions they deemed as possibly stress reducing in epileptic or PNES populations. All studies included measurements for seizure frequency and perceived stress using a self-report method. All studies used a control group, with the use of active/passive control group being evenly distributed among studies. Haut et al. (2018) used an active control, and Novakova et al. (2019) used a control group in the form of a 1-month delayed intervention group.

Interventions and outcomes: In total, 2 outcomes were assessed among studies, being seizure frequency and self-reported stress. Novakova et al. (2019) used a self-help workbook designed with methods to lower stress, a significant reduction in self-reported stress $t(28) = 2.74$, $CI = .95$, $p = .01$, with a medium effect size ($dz = .51$) was observed one-month postintervention in the study. The effect size was summarized using the mean difference between pre- to post-intervention with a 95% confidence interval. No statistically significant changes to seizure frequency or any other measurement except self-perceived stress was found. Haut et al. (2018) used Progressive Muscle Relaxation (PMR) as the intervention and Focused Attention (FA) as the control condition, a statistically significant reduction in seizure frequency in both the intervention group and active control group after the 12-week intervention period was found compared to the 8-week baseline, with 29% reduction in PMR group vs 25% reduction in Focused Attention group; $p = .38$; $CI = .95$. Over the 8-week baseline period, seizure trajectories did not differ across treatment groups ($p = .61$), and the rate of change in seizures was stable ($p = .84$). During the treatment phase, the rate of change in seizures was again similar across the 2 treatments ($p = .76$) with both groups showing a decrease in seizures over time ($p < .0001$). PMR and Focused Attention did not differ in seizure reduction, although PMR was associated with a higher amount of stress-reduction relative to Focused Attention ($p < .05$).

A summary of the main characteristics of all included studies is provided in Table 1. A summary of the assessments used and the main findings in all included studies can be found in Table 2. In all studies, the self-reported measurements showed a statistically significant effect favoring stress-reduction interventions compared to the control interventions to lower participants perceived amount of stress post-intervention. A statistically significant reduction in seizure frequency compared to baseline was only observed in one of the included studies.

4. Discussion

The aim of the present systematic review was to assess stress-reduction interventions effects on seizure frequency and self-perceived stress among an epileptic population. The systematic review allowed me to select 2 controlled interventions studies conducted with adults, that had been diagnosed by a physician, with the vast majority of total participants being diagnosed with epilepsy (91.2%), and, 8.9% were diagnosed with psychogenic non-epileptic epilepsy (PNES). Across the collected studies, the efficacy of the interventions was assessed by means of self-report methods.

My hypothesis when conducting this systematic review was that stress-reduction based interventions would show a statistically significant effect on lowering self-reported seizure frequency among epileptic, and also lower epileptics levels of self-perceived stress. Based on the evidence collected from this systematic review, behavioral interventions that had labeled themselves as stress-reduction interventions did lower self-perceived stress among epileptics but did not show any statistically significant effects on lowering seizure frequency compared to control. Haut et al. (2018) conclude in their study that daily stress was not a predictor of seizures, which goes against the study by McKee & Privitera (2017) where stress was ranked as the most common precipitant for generating epileptic seizures by people with epilepsy. Haut et al. (2018) also concluded that even though statistically significant lowering of seizure frequency was observed, the active control showed similar results as the intervention, which further goes against my previously stated hypothesis. Why the active control group showed the same effects on seizure frequency as the intervention group might have been the case since the active control used Focused Attention training, a mental exercise that is a part of the psychobehavioral treatment Mindfulness-based stress-reduction, which shown efficiency in lowering seizure frequency (Haut, Gursky, & Privitera, 2019; Tang et al., 2014).

Novakova et al. (2019), conclude that participants reported a significant reduction in the amount of self-perceived stress post-intervention, but not did report any significant effects on seizure frequency. Even though the results from this systematic review goes the results of McKee &

Privitera (2017), and says that epileptics conception of stress being a precipitant for generating epileptic seizures is wrong, there is a strong caution interpreting these findings in any strong manner because of the very small set of studies that I was able to include. Strengths of the included studies would be their methodological presentation of the interventions conducted in each study and the included participants all being selected from epilepsy centers and neurology clinics, and been diagnosed by a physician. The study by Novakova et al. (2019) was the one study where there was no set amount of time for participants to practice their stress-reduction intervention that was informed of an unguided self-help intervention in form of a brief A5 booklet. Adherence was not formally assessed in the study. The authors concluded that some participants thought the self-help booklet intervention was too detailed and complex and suggested that it would have been helpful to have someone guide them through it. These factors might have made it so people did not follow through with their self-help interventions, and also since there were no explicit rewards or punishments with following through and actually doing the exercises. 16.9% of participants in the study had been diagnosed with PNES and not epilepsy. This might have had an effect on the results, but since the sample of PNES was so small the authors could not create a meaningful subgroup. The rate of participants failing to return follow-up information at both one- and two-month follow-ups being 52%, with participants that did follow-up being older adults, which might have skewed the results. The sample size was assessed as small in all studies by the authors, increasing the likelihood of a type II error (Haut et al., 2018; Novakova et al., 2019; Nunnally, 1960). Finally, these studies relied on self-report measures. With self-report questionnaires being prone to a number of recall and response biases (Howard, 1980).

The total of 2 studies in this systematic review is extremely low, this is likely because of the search terms used. Instead of searching for studies were the authors themselves has labeled the interventions as stress-reducing in nature there are several different approaches to choose from. One can instead search amongst 3 different approaches within stress-reduction, e.g., a mind-body approach or a cognitive-behavioral approach to reducing seizure frequency and see its effects on perceived stress among patients (Tang et al., 2014). One can also search for specific pre-set interventions during their search procedure from the beginning as well. I was contemplating using this approach during my search procedure and had already chosen 6 interventions to search for, e.g., Mindfulness-based stress-reduction, with all interventions having about 4 synonyms on average, e.g., MBSR, mindfulness, vipassana, and open-monitoring meditation. This approach to search for specific interventions from the beginning can be seen in the recent systematic review published this year in April “Behavioral interventions in epilepsy” by Haut et al. (2019). In this review, the authors

address recent behavioral clinical trials in epilepsy including cognitive behavioral therapy (CBT), mindfulness, progressive muscle relaxation (PMR), and self-management (Haut et al., 2019). In the review several behavioral treatments were reported as being efficient in improving seizure control, interventions included Mindfulness-based stress-reduction, PMR, yoga, et al. The authors summarise that behavioral treatments can be successful in lowering seizure frequency and are likely underutilized in the treatment of epilepsy. The authors concluded with stating that behavioral interventions for seizure control should be researched more and that appropriately chosen behavioral therapies could be important adjuncts to standard therapy by motivated and interested patients.

4.1 Conclusion

In summary, this systematic review provides results stating that the correlation between self-perceived stress and seizure frequency is not statistically significant and that stress might not be a risk-factor to generate seizures. Although these results go against goes against previous theory (McKee & Privitera, 2017; Novakova et al., 2013; Tang et al., 2014) there is a very strong caution interpreting these findings in any strong manner because of the very small set of studies that I was able to include. It would not be warranted state that stress-reduction interventions cannot help aid as a complementary treatment to anti-epileptic drugs for an epileptic population in this systematic review mainly cause the very small set of included studies in this systematic review. Future suggestions would be more and larger double-blinded trials to truly conclude if stress-reducing behavioral treatment could become a staple as a complementary treatment for epileptics on an international level. I still consider stress-reduction interventions a possible way for motivated epileptic patients to help control their seizures based on previous data and newly found evidence found in the systematic review by Haut et al., (2019). I refer readers interested in the subject to read the recent review by Haut et al., (2019) if interested in reading more about behavioral treatments efficiency on reducing seizure frequency among epileptics.

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