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Review

Stress regulation in drug-resistant epilepsy

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ABSTRACT

The prevalence of psychological distress, especially depressive and anxiety disorders, is higher in epilepsy than in other chronic health conditions. These comorbid conditions contribute even more than epileptic seizures themselves to impaired quality of life in patients with epilepsy (PWE). The link between these comorbidities and epilepsy appears to have a neurobiological basis, which is at least partly mediated by stress through psychological and pathophysiological pathways. The impact of stress in PWE is also particularly important because it is the most frequently reported seizure trigger. It is therefore crucial for clinicians to take stress-related conditions and psychiatric comorbidities into account when managing PWE and to propose clinical support to enhance self-control of stress. Screening tools have been specially designed and validated in PWE for depressive disorders and anxiety disorders (e.g. NDDI-E, GAD-7). Other instruments are useful for measuring stress-related variables (e.g. SRRS, PSS, SCS, MHLCS, DSR-15, ERP-R, QOLIE-31) in order to help characterize the individual "stress profile" and thus orientate patients towards the most appropriate treatment. Management includes both pharmacological treatment and nonpharmacological methods for enhancing self-management of stress (e.g. mindfulness-based therapies, yoga, cognitive-behavioral therapies, biofeedback), which may not only protect against psychiatric comorbidities but also reduce seizure frequency.

1. Introduction

Unpredictability of seizures remains one of the most disabling aspects of epilepsy, but comorbid disorders may have an even more important contribution to impaired quality of life (QOL) in patients with epilepsy (PWE). Among epileptic comorbidities, psychiatric disorders are in the foreground, especially depressive disorders and anxiety disorders [1]. Prevalence of these disorders is higher in epilepsy than in other chronic diseases [2] due to specific psychophysiological and neurophysiological mechanisms, especially those involved in stress responses [3]. From a psychological perspective, it is conventional to conceptualize depression and anxiety in epilepsy as indicating a heightened emotional response in response to the unpredictable nature of seizures, and to the restriction of activities resulting in low self-esteem, stigma and social rejection. In addition, stress is frequently identified by patients as a precipitant factor of seizures [4]. As well as this psychological model there is also a well-established neurobiological model of depression and anxiety, which is useful to consider in the context of epilepsy. The pathophysiological links between stress, depressive disorders and anxiety disorders are well-known. Animal models provide accumulating evidence that epileptic activity alters the neurophysiological pathways involved in stress responses, and that stress response also affects epileptic activity [5].

Identifying and managing depressive and anxiety disorders and stress has been highlighted as a crucial issue in patients with epilepsy (PWE), with a need to individualize treatment according to individual patient profiles [6]. In the present article we aim to present an overview of current knowledge of stress and epilepsy and then focus on the various health psychology tools available for characterizing patient profiles of depression, anxiety and stress and their capacity to cope with these. We will also discuss the different stress management therapies currently available for PWE, and reflect on how patient profile might influence choice of therapy.

Abbreviations: AED, Anti Epileptic Drug; MDD, Major Depressive Disorder; GAD, Generalized Anxiety Disorder; QOL, Quality of Life; PWE, Patient With Epilepsy; TLE, Temporal Lobe Epilepsy; PSC, Perceived Self-Control; LOC, Locus Of Control.

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1.1. Stress, depressive and anxiety comorbidities and epilepsies

General understanding has emerged about the role of stress in the etiology and maintenance of psychopathologies [7]. The prevalence of psychological distress is higher in epilepsy compared to other chronic health conditions [2]. Many clinical and epidemiological studies have shown high proportions of PWE suffering from psychosocial difficulties directly linked to emotional and cognitive disorders [8]. Major depressive disorder (MDD) and generalized anxiety disorder (GAD) are the two most prevalent psychiatric comorbidities in PWE [1] and particularly in temporal lobe epilepsy (TLE) [9]. In addition, it has been suggested that these psychological comorbidities can precede the onset of seizures [10]. This observation indicates a possible bidirectional relationship and it has been postulated that some shared neurobiological mechanisms exist underlying epilepsy, depression, anxiety and vulnerability to stress [11,12]. Epilepsy is the cause of an important burden on quality of life with frequent impairment in social functioning that can be explained largely by comorbid depression and anxiety. Indeed, stress plays a key role in the onset of depression and anxiety disorders and is known to worsen these conditions. Stress is also frequently described as a factor precipitating seizures, or even as the trigger for development of epilepsy. Neurological and endocrine pathways of stress regulation are known to be impaired in epilepsy, especially in TLE [5] and ongoing research aims to better characterize the interactions of stress and epilepsy from a neurobiological perspective.

1.1.1. Major depressive disorder and anxiety disorder comorbidities in epilepsies

1.1.1.1. Major depressive disorder. MDD is the psychiatric comorbidity the most frequently associated with epilepsy [13,14]. Between 30% and 35% of PWE suffer from depression during their lives [13]. The proportion is highest in refractory epilepsies, accounting for 20% to 55% of drug-resistant patients compared to 3% to 9% of patients with good seizure control [8]. The prevalence of depression in drug-resistant epilepsy is 10 times greater than the general population [8]. Thus, MDD represents a global problem in PWE [15,16]. The existence of neurobiological mechanisms common to MDD and epilepsy could explain this high prevalence. Presence of MDD is associated with greater risk of unprovoked seizure [17]. Moreover, the presence of MDD in PWE is associated with a negative effect on seizure control [18], higher rates of adverse effects of antiepileptic drug (AED) therapy [19], poorer outcome of epilepsy surgery [20,21], lower quality of life [22], increased risk of suicidal behavior in PWE [23], and increased health care costs [24].

1.1.1.2. Anxiety and generalized anxiety disorder. Anxiety is described as a phenomenon that may occur in the ictal, postictal or interictal state [25]. Studies founded that the risk of anxiety disorders is higher in TLE than in other types [26,27]. These observations are supported by neurobiological mechanisms [5]. Nevertheless, the prevalence of anxiety disorders depending on the type of epilepsy is not so clear. Indeed, Swinkels et al. [28] showed that if the persons suffering from TLE are more likely to suffer from anxiety disorders (25% to 30%) than the general population (12% to 19%), they do not differ from other types of epilepsy.

Anxiety comorbidities can be classified into:

- interictal anxiety disorders, which are not chronologically linked to the seizure. The characteristic forms of DSM-5 and forms specific to the epileptic context are distinguished. According to DSM-5, interictal anxiety disorders can be characterized in order of prevalence in epilepsy as: generalized anxiety disorder (GAD) (3% to 13%, with an even higher prevalence in patients with drug-resistant epilepsy) [29]; obsessive–compulsive disorder (1% to 3%); and post-traumatic stress disorder (1% to 5%) [30].
- ictal anxiety disorders, which are directly related to the occurrence of seizures, in which anxiety is distinguished as either a prodromal symptom, a preictal phenomenon, a predictor of a seizure, or as a postictal symptom following a seizure.

Anxiety is sometimes described as a psychological response that is exacerbated in response to the unpredictable nature of seizures, and to restriction of life activities resulting in low self-esteem, stigmatization and social rejection [27]. Anxiety can also be conceptualized in neurophysiological and neurobiological terms; for example, psychosocial stress in the form of chronic anxiety has been described as a dysregulated physiological response of the organism to perceived unsafe conditions [31]. The main factors associated with anxiety are not necessarily epilepsy-related, since they concern history of depression, educational level, unemployment or female gender, chronic ill health, perceived side effects of antiepileptic medication but not the duration of epilepsy [32]. A personality trait of anxiety should be considered as a premorbid condition and is also one of the main factors determining QOL in epileptic patients [33].

Anxiety is described in terms of a specific disorder when particular psychiatric criteria are present. In particular, generalized anxiety disorder (GAD) is the second most frequent psychiatric disorder in PWE after MDD [1,34–36]. GAD is characterized by disabling and persistent free-floating worry. Occurring in the context of epilepsy, GAD is often associated with fear of future seizures, fear of disease progression, or fear of specific complications [25,37]. As for MDD, the presence of GAD in PWE is associated with a negative effect on seizure control [18,20,38], higher rates of adverse effects of AED therapy [19,39,40], increased risk of suicidal behavior in PWE [23,41,42] and lower QOL [22,43], as well as increased health care costs [24].

1.1.2. Stress in epilepsies

1.1.2.1. Stress: definition

1.1.2.1.1. The physiological model of Selye. Stress response and stressful events are often confounded. In addition, the issue of whether the stress response becomes chronic (and maladaptive) is highly relevant to clinical effect. In order to clarify the use of "stress", the following terminology will be used: stimuli that are seen as a source of stress are referred to as "stressful events" and the psychological, neurophysiological and/or biological responses to the stressful events are referred to as "stress responses". Stress responses are adaptive processes, the purpose of which is to restore homeostasis. However, prolonged or intense exposure to stressful events leading to prolonged stress responses can potentially lead to tissue damage and disease. In addition, depending on characteristics of the individual in terms of their resilience and vulnerability to stressful events, the stress response may be more or less exaggerated and/or prolonged [31]. From the physiological point of view stress is a variable arising from the physical or social environment. Cannon [44] introduced the idea that an organism's homeostasis can be threatened by an aversive situation. Homeostasis refers to the normal resistance (or equilibrium) level of the organism. The purpose of physiological changes in response to stress is to leverage resources in order to cope with the stressful event and to return to the homeostatic state. The term stress was used by Selye [45] to characterize the physiological changes and responses occurring when the homeostasis is disturbed. Selye [45] introduced the first model of stress with his General Adaptation Syndrome in which he described three stages: alarm stage, resistance stage and exhaustion stage. Alarm stage is the first reaction to a stressful event exposure. Homeostasis is disturbed, physiological resources are mobilized in order to flight or fight the stressful event. Resistance stage is an adaptation stage. The resources are restored to return at the homeostatic state in order to the organism could deal with others stressful events. The exhaustion stage appears when the stressful event occurs in long duration or strong intensity, so resources cannot be restored. Building on Selye's work, a recent model [31] has conceptualized chronic stress (and chronic anxiety) in terms of the innate default state

of readiness of all organisms to produce a stress response, which when not required must be appropriately inhibited by prefrontal-limbic circuitry. Dysfunction of perception of and/or reaction to signals relating to safety of the individual in his or her current environment may therefore lead to a chronic state of perceived unsafety, accompanied by physiological and psychobehavioral responses to this. This has been termed the "Generalized Unsafety Theory of Stress (GUTS)" [31].

1.1.2.1.2. Psychological health model: perceived stress, perceived self-control, coping. From the psychological health point of view, stress is not only defined by physiological reactions to stressful events. Several models have been proposed to describe the relationship between stressful events and individual responses. All of them agree that stress responses depend on the interaction between the stressful events and individual and situational components [46]. According to this conception, stress responses depend on perceived stress, perceived self-control (PSC) and coping. Perceived stress is a subjective evaluation of an aversive situation. Perceived self-control is the subjective evaluation of the resources someone has about in a given situation and determines if the situation is perceived as a challenge or a threat. Coping refers to the strategies that the subject develops in order to reduce the impact of stressful events on his or her life. Perceived stress, PSC and coping are influenced by main factors related to dimensional personality traits of the subject. Perceived stress is influenced by the personality trait of anxiety. PSC is influenced by the belief that one's own capacities and actions can influence one's environment, situation or a desired result [47]. These beliefs are collectively called locus of control (LOC). Coping is influenced by PSC [48], but also by resilience that fundamentally refers to a positive adaptation, or the general ability to deal with challenging or threatening situations with maintaining or regaining mental health [49]. All these variables can be associated with lower reactivity to stressful events [50]. Having a sense of control during stress can limit the excitation reactions, the stress hormone release or the arrival of maladaptive behaviors like panic [51]. In this regard, stress responses result from an imbalance between perceived demand and perceived capacities to respond.

1.1.2.2. Stress and epilepsy. In the field of psychopathology, it is well established that stress is a mean mediator of MDD and anxiety disorders. Two distinct mechanisms have been highlighted: *sensitivity* and *sensitization* [7]. *Sensitivity* refers to personality trait resulting from a relationship between genetic characteristics and the early contextual environment. Stress *sensitivity* exists prior to the development of psychopathology [52,53]. *Sensitization* occurs through repeated exposure to stressful events. Over time even minor events could be perceived as stressful and participate in triggering and maintaining the disorder [54,55]. Both these mechanisms are also involved in the triggering and the maintenance of epilepsy: epileptogenesis via *sensitivity* and seizure occurrence via *sensitization*. There are clinical and neurophysiological arguments suggesting a link between stressful events and epilepsy or seizure onset. This link should be supported by dysfunctions in physiological stress responses and a perceived stress vulnerability conducting PWE to overreact to stressful events (Fig. 1).

1.1.2.2.1. Stress as epileptogenesis factor. A link between the onset of epilepsy and stressful events has been proposed. This has not so far been extensively studied in humans but rodent models are in favor of this hypothesis [56]. Prenatal and postnatal stress exposure has been shown to increase seizure susceptibility in animal models [57]. In rat pups in which chronic early life stress was induced by unpredictable and fragmented nurturing behavior of the mother, epileptic spikes were observed in the majority of them within the next few weeks. Moreover, 48% developed behavioral events resembling human epilepsy infantile spasms and 9% developed limbic seizures involving amygdala [58]. A recent study on adult rats, [59] have shown that social defeat produced in 50% of rats reduced threshold for status epilepticus, accelerated epileptogenesis, and once epilepsy was induced, depression-like profile and cognitive deficits. Low serum brain-derived neurotrophic factor (BDNF) levels measured before status epilepticus identified this vulnerable population. These results indicate a possible effect of chronic early-life stress on developing brain excitability that may favor epileptogenesis. In human, the data are limited and do not lead to an objective relationship between early-life stress and epileptogenesis. A study investigating the effect of prenatal stress on epileptogenesis found no link between the loss of a close family member in pregnant women and epilepsy onset in their offspring, compared to unexposed children [60]. Similarly, no link between parental stress within one year before the pregnancy and febrile seizures in childhood was observed [61]. On the contrary, the loss of a child as a stressful event is associated with an increased risk of epilepsy diagnosis in the next years compared with parents who had not lost a child [62]. Recently, in a cohort of 4618 PWE, 22 reported a major stressful life event as the trigger of their epilepsy. These stressful events were mainly death of someone close. Other patients reported a broken relation of trust, a sentimental separation, or been subject of violence [63]. During the 8-week period after the Great East-Japan earthquake in March 2011, the number of patients with unprovoked seizures was higher than the same period in the three past years, suggesting an association between stressful event and seizure occurrence [64]. In the study of 31 patients with drug resistant TLE [65], it was reported that 9/31 patients started their disease in a context of a stressful event, all belonging to the "emotionally vulnerable" group.

However, all these studies considered only the nature of the stressful event, not the patient's perceived stress, and also did not take into account the eventual chronicity of the stress response.

1.1.2.2.2. Stress as seizure trigger factor. Subjective identification of at least one potential triggering factor affecting the likelihood of seizure onset has been reported by 60% to 70% of patients [66,67]. Stressful events are the most frequently reported by PWE in general [4] and more particularly in those with TLE [66,68]. Lanteaume et al. [65] used the term "emotional vulnerability" to define this particular sensitivity to stress as a seizure precipitant in PWE. However, the existence of specific neurobiological factors underpinning emotional vulnerability remains uncertain. Differences have been however shown in a positron emission tomography (PET) study. Indeed, data obtained in TLE patients with emotional vulnerability in comparison with patients not reporting sensitivity to stressful events depicted more marked changes in amygdala-related networks [69] and a correlation between PET changes and emotional bias measures. Levels of anxiety in PWE tended to be linked with self-reported seizure precipitants [70]. A high level of anxiety could itself act as a precipitant factor through neurophysiological and hormonal alterations related to the impact of stress hormones on neuronal excitability and thus seizure susceptibility [5]. On the other hand, patients with high anxiety levels could also be more likely to seek explanations for the onset of their seizures. Moreover, it is difficult to determine whether experiencing stress or anxiety is the seizure precursor, or whether it is rather the feeling of an impending seizure that increases the level of stress and anxiety; indeed, both mechanisms could co-exist. If relationship between stressful events and seizures is not established, the fact that patients spontaneously report them as precipitant factor show their importance in the disease as perceived stressful events. Possibly, an important factor that clinicians should deal with to help PWE to cope with epilepsy is perceived stress.

Some authors have also pointed at a possible antiepileptic effect of acute stress [71–73]. Indeed, patients reporting stress as triggering factor often describe that the seizure occurs after the stressful event, just when they calm down. It can be hypothesized that the increased activation of the peripheral sympathetic nervous system (SNS) induced by stress increases the threshold of the risk of triggering a seizure [74]. The imbalance of arousal of the SNS between the stressful moment and after, could possibly lead to triggering seizures. Studies are needed to investigate this hypothesis. However, clinical arguments with biofeedback on electrodermal activity (EDA biofeedback) shown that

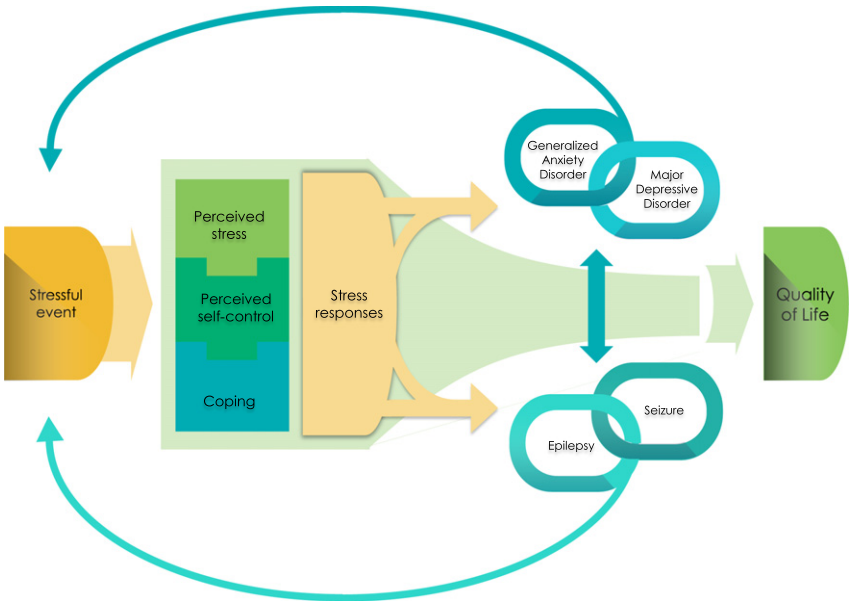

Fig. 1. A model of stress in patients with epilepsy. Stressful events could be triggers of both epilepsy and seizures and also of anxiety and depressive disorders associated with epilepsy. However, the importance of stress responses are determined by the association of perceived stress (PS), perceived self-control (PSC) with regard to the stressful event and the individual strategies to cope with it. An association of high PS, low PSC and poor coping strategies will lead to high stress responses and decrease the threshold of triggering epilepsy, seizures, anxiety and depressive disorders which are by themselves stressful events. On the contrary, low PS, high PSC and appropriate coping strategies will lead to less risk of seizures and associated disorders and to a better quality of life. Perceived stress is influenced by anxiety trait of the subject, perceived self-control by the locus of control, and coping via resilience.

increased peripheral sympathetic arousal lead to decrease the seizure threshold [74,75].

1.1.2.3. Links between stress, MDD and anxiety disorders and epilepsy

1.1.2.3.1. The diathesis stress model. Stress has long been known as a triggering factor for depressive and anxiety disorders. However, not every individual is equally sensitive to stress. This idea is described by the diathesis stress model. Diathesis refers to a vulnerability to stress depending on genetic, biological, cognitive and early-life factors. According to this model, a severe stress episode associated with a weak diathesis can lead to psychiatric disorders; whereas for people with a strong diathesis, even a minor stress can be sufficient to trigger these disorders. This model could also help explain the link between stress, epilepsy and depressive and anxiety comorbidities. Early life stressful events are important factors in the diathesis of psychiatric comorbidities, and perhaps also of epilepsy onset and of seizures for PWE. Indeed, patients with stress-triggered seizures (effect of acute stress) are more likely to have been subjected to early life stress, particularly emotional abuse [76]. It has been shown in rats that such events may have long-lasting effects on brain excitability and may contribute to increased risk of triggering seizures and development of epilepsy [58].

In PWE, it seems likely that there are differential effects of both acute and chronic stress, with chronic stress being associated with increased psychological comorbidities (and possibly affecting epileptogenesis) over the long-term; and acute stress in some PWE leading to increased seizure risk in the short–term. The relative balance of these two aspects would contribute to the "stress profile" of an individual patient.

1.1.2.3.2. Neurophysiological evidence. The comorbid occurrence of epilepsy, MDD and anxiety disorders is underpinned by neuroanatomical and neurophysiological mechanisms. Several clinical and animal studies support the relationship between stress and seizures by highlighting the impact of stress hormones on neuronal excitability and the susceptibility to seizures [5].

The relationship between stress and epilepsy was suggested by the finding that the rate of stress hormones is generally higher for PWE and that it increases after a seizure [77]. An increase in the frequency of seizures is associated with an increase in cortisol levels [78]. Anatomically the stress response is modulated by the hypothalamic-pituitary-adrenal axis (HPA axis) which is partly regulated by the negative feedback structures generally involved in the genesis of seizures in TLE: the amygdala and the hippocampus. On the other hand, dysregulation of the HPA axis is a characteristic of disorders linked to stress, depression and TLE. This axis hyperactivity is observed in MDD [79], in anxiety disorder [80] and epilepsy [81]. Adreno-corticotropin and corticosterone (two hormones involved in stress) have the effect of increasing the excitability of neurons in the hippocampus and may thus be involved in the onset of seizures [82]. A relationship between cortisol levels and epileptiform discharges has recently been observed in patients with stress-sensitive seizures, suggesting an influence of stress hormones on epileptic activity [83]. Stress could trigger seizures through two different mechanisms. The first is a reflex-like mechanism, in which stress is a triggering factor. The seizure is triggered by neuronal hyperexcitability related to emotional bias of maintained attention to threatening information [69]. The second corresponds to a temporally slower mechanism in which stress can be considered as a predisposing factor. The seizure is favored by chronic stress perceived in the hours or days preceding the seizure, which can be mediated by ultradian hormonal variations in HPA axis [83].

Other physiological data highlight a neuroanatomical link between stress, MDD, anxiety disorders and epilepsy. In animal models, data suggest that a stressful event may favor MDD and epileptogenesis. A population of adult rats vulnerable to develop a depression like-profile induced by a stressful event has been identified by low levels of serum brain derived neurotrophic factor (BDNF) compared to non-vulnerable ones [84]. In addition, in rats exposed to a stressful situation and kainic acid (status epileptic inductor), only those in which serum BDNF levels did not return to control levels 2 weeks after the stress exposure developed the depression-like profile [59]. In humans, MDD and anxiety disorders are negatively correlated to serum BDNF levels [85] and BDNF levels remain lower in patients with MDD than in healthy control subjects even after remission [86]. Data on BDNF levels in PWE remain controversial and relatively little studied with studies showing variable results. One study showed no difference in baseline BDNF level compared to a control population, but a correlation between the serum

level of BDNF and epilepsy severity [87]; another found a reduction in BDNF in PWE compared to control groups [88]. However, correlations with comorbidities of epilepsy remain unknown. A recent study seemed to indicate some relation between BDNF levels measured in situ in the hippocampus, and the treatment of MDD in TLE [89].

1.2. Clinical evaluations of MDD and anxiety disorder comorbidities and stress in epilepsy

The links between MDD, anxiety disorder, stress and epilepsy have been studied both neurophysiologically and clinically. With the help of appropriate clinical tools, epidemiological studies have shown the importance of the prevalence of comorbid psychiatric stress-related disorders in epilepsy and so the importance of detecting and appropriately managing them. These tools are useful for the clinician in terms of screening or help with orientation towards an appropriate clinical management approach.

1.2.1. Screening of comorbidities

1.2.1.1. Screening for major depressive disorder. Despite the significance of MDD in epilepsy, clinicians still underestimate its importance [90,91]. While multiple pre-existing screening questionnaires for depression have been tested for their validity and usefulness in PWE with varying results [92,93]. The Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) was developed with the specific aim of detecting MDE in PWE [90] (Table 1). The NDDI-E is a reliable and practicable screening instrument that help to improve detection of MDE in PWE. The NDDI-E is a self-reported questionnaire based on 6 items. It was specifically developed to minimize potential confounding effects due to seizures, cognitive consequences of epilepsy and antiepileptic treatments, which might produce symptoms overlapping with those of MDE [90,94]. It is a shorter questionnaire than classical self-reported screening questionnaires to detect MDE, such as the Beck Depression Inventory (BDI, 21 items) or the Center for Epidemiologic Studies Depression Scale (CES-D, 20 items), both of which have been validated in PWE (Jones et al., 2005). Thus, the NDDI-E is a more time-efficient means of detecting MDE, which improves the ability to detect MDE in PWE in busy clinical practice [95]. The NDDI-E has now been translated into and validated in many languages [96]. Thus, the NDDI-E represents a multi-lingual diagnostic tool for the worldwide problem of MDE in PWE [15].

1.2.1.2. Screening of generalized anxiety disorder. As is the case for MDD, GAD in PWE is clinically underestimated [97] (Table 1). The Generalized Anxiety Disorder 7 (GAD-7) was validated to detect GAD in PWE [98,99]. The GAD-7 is a reliable and practicable screening instrument that helps to improve detection of GAD in PWE. The GAD-7 is a self-reported questionnaire similar to the NDDI-E and based on only a few items. The GAD-7 is particularly well suited as a screening tool in PWE since it contains no somatic items that might be confused with symptoms related to epilepsy or AED [97]. Moreover the GAD-7 provides complementary information to the NDDI-E [29]. It is a shorter questionnaire than classical self-reported screening questionnaires for GAD [100–102], which helps to optimize its use in a busy clinical practice. The GAD-7 has been translated into and validated in Korean and Chinese [98,99], in Spanish [103] and in French [29]. The translation and validation in other languages has been promoted by the ILAE in order to make the GAD-7 a worldwide instrument similar to the NDDI-E [104]. At this time, specific screening tools for other anxiety disorders occurring in PWE are not yet available.

Although the NDDI-E and the GAD-7 measures present high acceptability, it can be considered too lengthy for some patients with epilepsy. Indeed patients with epilepsy may have cognitive deficits making even relatively short questionnaires challenging to complete. A ultra short form would enable its use to be increased, in line with the revised version of the World Health Organization's classic principles of screening [105] that now highlights the need for "equity and access to screening for the entire target population" [106]. Such ultra short forms (two items of the NDDI-E and one item of the GAD) have been recently validated in patient with epilepsy [107].

1.2.2. Measures of stress

Some psychometric tools are of particular interest to help clinically evaluate the patient's exposure to stressful stimuli and his spontaneous adjustment capabilities. They can also be used before and after interventions such as cognitive behavioral therapy (CBT) to assess therapeutic impact. Tools such as the Social Readjustment Rating Scale (SRRS) (which evaluates stressful events) [108] or the Perceived Stress Scale (PSS) [109] are useful to assess the impact of stress on the disease and the patient's quality of life in order to guide towards therapeutic strategies primarily targeting this issue. Evaluation of PSC over the disease through the Self-Control Schedule (SCS) [110] or the Multidimensional Health Locus of Control Scale MHLCS [111] may point to a method to increase the sense of control. Scales investigating coping strategies, such as Emotion Regulation Profile-Revised (ERP-R) [112], highlight the spontaneous adjustment strategies and can direct therapeutic work throughout CBT for example. Within the context of CBT, the information gathered with the Quality of Life in Epilepsy Inventory (QOLIE-31) [113] could adapt the therapy based on the most relevant issues. Finally, building upon the strengths of the person, with the dispositional Resilience Scale – 15 (DSR-15) [114], can be an asset for optimal support (Table 2). (See Table 3.)

1.2.2.1. Social readjustment rating scale (SRRS, Holmes & Rahe, 1967). The SRRS [108] is a 43 item scale and examines recent life experience and includes items relating to professional (dismissal, change of job) or personal (marriage, birth, bereavement, moving), financial (difficulties, loan), social (religious practice, relations), or physiological (illness, sleep, food) changes. According to the authors, decrease in disease resistance can be attributed to the occurrence of stressful events. In TLE scores are correlated with anxiety trait [115] and several studies shown a link between stressful life events and epilepsy [64,116,117]. While this scale is an instrument of indirect measurement of stress and does not measure the intensity or the subjective experience, it remains a relevant tool to anticipate resistance to disease.

Table 1
Selected MDD and GAD screening short instruments.

Domain	Measure	Items and scoring	Evidence supporting use
Major depressive disorder	Neurological Disorders Depression Inventory for Epilepsy (NDDI-E; Gilliam, Barry, et al. 2006)	6 items to assess depressive symptoms and specifically developed to minimize potential confounding effects due to seizures, cognitive consequences of epilepsy and antiepileptic treatments.	Specificity range from 0.78 to 0.94 and sensitivity from 0.80 to 0.93 according to language format. Threshold usually >15 except in Spain, Italy and German (>13), in Korean (>11) and in Japan (>16)
Generalized anxiety disorder	Generalized Anxiety Disorder - 7	7 items to assess anxiety generalized symptom without somatic items to minimize potential confounding effects due to seizures and antiepileptic treatments	Specificity range from 0.76 to 0.94 and sensitivity from 0.92 to 0.96 according to language format. Threshold usually >6 or >7.

1.2.2.2. Perceived stress scale (PSS, Cohen et al., 1983). The PSS is a 14 item scale based on the psychological-health approach of stress by Lazarus & Folkman, which describes a situation as stressful when it is perceived as threatening, unpredictable and uncontrollable. The PSS is the most widely used psychological tool for measuring the perception of stress. The questions in the PSS asked about the feelings and thoughts of the patients during the past month. Each item is rated on a 5-point scale ranging from never (0) to almost always (4). The higher the total score, the higher is the perceived stress level. A high score of perceived stress predicts more somatic and psychiatric symptoms and greater use of health care services. PSC is an interesting variable to investigate because its benefits for health even exist in the absence of effective control over aversive events [118]. In epilepsy PSS scores are linked with perceived social stigma [119], nonadherence with medication and change in depression scores over time [3].

1.2.2.3. Self-control schedule (SCS, Rosenbaum, 1980). SCS is a 36 item scale evaluating PSC in four dimensions: cognitive ability to control emotional and physiological sensations; the subject's employment of problem-solving strategies; personal ability to delay immediate gratification; and perceived self-efficacy. Items are scores on a 6 point Likert scale from +3 "very characteristic of me", to −3 "very uncharacteristic of me". The scores correlate with LOC and "irrational beliefs". In the 600 subjects of the validating cohort, those scoring high on the SCS were found to have an Internal Locus of Control and to hold fewer "irrational" beliefs compared to those scoring low. No clinical studies have used this tool to evaluate self-control in PWE but it would be interesting to investigate emotional vulnerability risks in these patients considering the link between self-control over seizures and anxiety disorders and MDD [120]. It seems that patients' perception of how they might be able to control their seizures and health strongly affects their well-being and quality of life [121]; therefore, orienting patients towards clinical management approaches aimed at improving self-control should be relevant for those with low PSC.

1.2.2.4. Multidimensional health locus of control scale (MHLCS, Wallston et al., 1978). MHLCS is used to measure health locus of control through 18 items, 6 items by each dimension of LOC (internal, external chance, external powerful others) presented in random order. All MHLC items were measured on 7-point unipolar scales, anchored by "strongly disagree" and "strongly agree". Internal HLC refers to the patient's point of view that his own actions are linked to his health. Inversely, patients with high external chance HLC tend to think that their health status is linked to nothing in particular and those with external powerful others HLC that other people, such as clinicians or family, are more involved than themselves. This scale has a great interest in clinical practice because health status has a positive correlation ($r = 0.40$) with I-HLC and negative correlation ($r = -0.28$) with C-HLC and particularly in PWE in whom the type of HLC is crucial in depression and anxiety levels [122].

1.2.2.5. Dispositional resilience scale — 15 (DSR-15, Bartone, 2007). The DSR-15 is composed of 15 items measured by a 4 point Likert scale. A global score of resilience is obtained, higher scores indicating higher resilience. Using 3 subscales with 5 item subscores, the type of resilience can be calculated in terms of commitment, control and challenge. In PWE, investigation of components of resilience and how these might be influenced them with clinical intervention would be interesting because resilience and QOL are interlinked. Indeed, QOL is a predictor of resilience [123] and resilience impacts on QOL [124].

1.2.2.6. Emotion regulation profile-revised (ERP-R, Nelis & al., 2011). The ERP-R (The Emotion Regulation Profile Revised) is a self-administered questionnaire that was constructed to evaluate the emotional regulation strategies or coping emotional regulation based on Gross's model [125]. It includes 15 different scenarios and participants must select reactions that reflect how they might react in similar situations to those presented. Emotional regulation as measured by ERP-R is highly correlated with emotional intelligence and personality. The ERP-R measures the regulation of negative and positive emotions. The ERP-R will help provide information on the functional or dysfunctional strategies the patient implements to cope with everyday life situations. Many studies have investigated the strong link between coping strategies, anxiety disorders, MDD and QOL in epilepsy [126–128]. This tool could be very helpful for orienting clinical supports for these patients, particularly for Cognitive-Behavioral Therapies (CBT).

1.2.2.7. Quality of life in epilepsy (QOLIE-31, Cramer et al., 1998). The QOLIE-31 [113] was designed to assess the quality of life in PWE using 7 subscales evaluating seizure worry, emotional well-being, energy/fatigue, cognitive functioning, medication effects, social functioning and overall quality of life. Responses are rated on several Likert scales including scales ranging from "worst possible quality of life" to "best possible quality of life" and items asking about how the patient feels ranging from "all of the time" to "none of the time". A total score is obtained by a weighted average of subscales scores, the higher is the score,

Table 2
Selected instruments to evaluate exposure to stress and adjustment capabilities helpful to orientate therapeutic approach and evaluate its efficacy.

Domain	Measure	Items and scoring	Evidence supporting use
Stressful events	Social readjustment rating scale (SRRS; Holmes & Rahe, 1967)	43 items, prioritized in accordance with the value of the item. Higher the score is, higher the item is considered as stressful	Give a probability of developing health issues
Perceived stress	Perceived Stress Scale (PSS; Cohen, Kamarck, & Mermelstein, 1983)	14 items to assess the frequency of events perceived as stressful	Validated on large heterogeneous population. Scores highly correlated with well-being indicators and somatic health
Perceived self-control	Self-Control Schedule (SCS; Rosenbaum, 1980)	36 items to assess individual perception of control	Validated on large population. Scores correlated on sensitivity to stressful events
Health locus of control	Multidimentional Health Locus of Control Scale (MHLCS; Wallston, Wallston, & DeVellis, 1978)	18 items to evaluate the type of control. 6 items for internal, 6 for external powerful others and 6 for external chance	Used in numerous studies of epilepsy. High internal reliability. Health status has a positive correlation with I-HLC and negative correlation with C-HLC
Resilience	Dispositional Resilience Scale - 15 (DSR-15; Bartone, 2007)	15 items to evaluate hardiness and type of resilience. 5 items for each type of resilience: commitment, control and challenge	Short, good internal consistency and validity
Coping	Emotion Regulation Profile-Revised (ERP-R; Nelis, Quoidbach, Hansenne, & Mikolajczak, 2011)	15 scenarios, 10 describing negative situations and 5 positive.	Ecological, qualitative evaluation
Quality of life	Quality of Life in Epilepsy Inventory (QOLIE-31; Cramer et al., 1998)	31 items in 7 subscales evaluating seizure worry, emotional well-being, energy/fatigue, cognitive functioning, medication effects, social functioning	Specifically designed for PWE

better the quality of life is estimated. The examination of the subscales scores is able to inquire about the fields in which epilepsy is the source of the most disabling handicap to the patient. QOLIE-31 is one of the most widely used scales to evaluate QOL in PWE. Scores are linked to alexithymia [129], MDD, anxiety disorders, seizure frequency, pharmacoresistance [130,131], and many other social components [19,37]. The main interest of this tool in clinical practice is to investigate which domain should be prioritized to deal with the patient.

1.3. Treatment of MDD and anxiety disorder comorbidities and stress in epilepsy

1.3.1. Treatments for comorbidities

MDD and anxiety disorder (in particular GAD) comorbidities of epilepsy have to be appropriately treated. The treatment has to be considered as similar for PWE and for patients without epilepsy, with the caveat that medications should be chosen with a view to avoiding adverse effects on seizure control or drug interactions with existing therapy; for example, selective serotonin reuptake inhibitors are much preferred over tricyclic antidepressants. For review, see: Ker et al. [132].

1.3.2. Stress management in epilepsy

1.3.2.1. Spontaneous stress regulation/coping style. Coping is generally described as the manner in which individuals handle stressful events. Coping strategies are designed to reduce the burden of the individual when he has to cope with stress or to control or tolerate a stressful situation. According to a classification of coping strategies, [133] those in which the subject is actively committed to assessing the problem and to handling the stressful situation (for example, using goal-orientated problem solving approach) are called "engagement" strategies. Engagement strategies can be emotion- or problem-based. Emotion-based coping strategies aim to regulate the emotion associated with a stressful event, while problem-based coping strategies are focused on the management of the event. Strategies of "disengagement" include those in which the subject attempts to move away from the person-environment interaction (i.e. denial, avoidance, distraction etc.) [134].

Strategies focused on emotions are frequently used by PWE [128]. This type of strategy, instead of directly coping with the problem, take the individual away from the source of the stress. In such cases acceptance, religion and social support are more often used as strategies while substance abuse, denial and humor are used less frequently [135].

PWE tend to use different coping strategies from the general population, using "disengagement" strategies [128]. There is a negative correlation between the use of engagement strategies, and self-assessment of the intensity of the seizures [129]; that is, a less active coping style in PWE has been found to be related to higher self-perceived seizure severity. In epilepsy, the personal coping style appears to be a better predictor of mental health aspects of QOL than are epilepsy-related variables. The mental component of health-related QOL is mainly explained by a passive coping style whose role is more important than seizure-related measures [136]. It has been shown that patients with epilepsy who adopt strategies of engagement, cognitive restructuring and problem-solving, have better psychosocial adaptation, better mental health, improved psychological well-being and decreased depression and anxiety. On the other hand, use of disengagement strategies had adverse consequences on social adaptation and was associated with higher levels of depression and anxiety, low self-esteem, intensified perceived stigma and reduced well-being [134]. Patients with higher levels of self-esteem, self-efficacy and QOL, with positive personal/family relationships and leisure activities use more control-based coping styles, while those with lower self-esteem, self-efficacy, reduced interpersonal/family contacts and recreational situations use more denial or exclusion strategies [137]. In addition, psychiatric comorbidities may impact the kind of coping strategies the patients use. Indeed, a greater use of escape-avoidance strategies is observed in relation with greater symptoms of both anxiety and depression. However, while anxious patients tend to use less distancing, depressed individuals use more self-controlling coping strategies than those who are not depressed [126]. In addition, more the patients are depressed, the more they use denial as a coping strategy [126].

1.3.2.2. Clinical approaches for stress management. A study comparing patients' and clinicians' opinions of different types of self-management program for stress showed dissonance between PWE and clinicians in their perceptions [138]. Interestingly in this study, significant differences were also found between perceptions of PWE who were essentially well in the inter-ictal period, with good mental health and cognitive function, compared to those with epilepsy and associated depression and/or cognitive impairment (termed "epilepsy plus" in this study). It is indeed the latter group that carries the burden of poor QOL and requires the bulk of healthcare services, so this observation of different patient needs and expectations within the broader group of PWE seems essential to take into account when planning and choosing management strategies. This study emphasized patients' demand for interventions based on learning coping strategies for the self-management of epilepsy, particularly when MDD and anxiety disorder are associated [138]. Various methods have been investigated to help patients to develop effective strategies to control seizures and improve quality of life including behavioral, cognitive or emotional approaches [139]. Some are considered as mind-body approaches (i.e. mindfulness, relaxation therapies, meditation and yoga) and others are based on management of cognition associated with emotions (i.e. biofeedback, cognitive-behavioral therapy). While the first group have great potential in chronic stress management, the second group may be more relevant for managing stress reflex responses (Table 3). All appear to have an effect on both patient well-being and seizure control [140–142]. All these methods are based on the observation of one's own mental state and physical activities, using attention training and process-oriented awareness. They are known to reduce perceived stress. Despite the lack of efficacy evidence, these various methods could be interesting adjunctions in the management of psychological outcomes frequently associated with epilepsy [143].

1.3.2.2.1. Chronic stress management: mind-body approaches

1.3.2.2.1.1. Mindfulness-based therapies. Mindfulness consists of voluntarily engaging and maintaining attention to internal or external experiences (feelings, thoughts, bodily sensations, etc.) at the present moment with acceptance and without value judgments [144]. Over the last decade mindfulness-based interventions have become well known in the management of chronic stress and can be useful in anxiety and depression treatment [145]. Converging evidence from functional neuroimaging and EEG studies of various meditation methods including mindfulness point to a neuroplasticity effect on neural circuits implicated in perception and emotional processing [146]. An improvement on subjective evaluations of stress measured by STAI and PSS was observed in stressed women after 8 weeks program of a mindfulness-based therapy. However, no differences were found on objective evaluation measured by cortisol levels [147]. In epilepsy, mindfulness-based therapy has recently shown a positive effect in both depressive and anxiety symptoms and seizure frequency [148]. Acceptance and Commitment Therapy is a psychological therapy using mindfulness skills and acceptance in order to induce behavioral and cognitive changes. It has shown an effect on seizure reduction and QOL improvement in 10 PWE after 12 h of therapy [149]. More recently, 60 patients with refractory epilepsy reported positive effects on depression, anxiety, quality of life, self-esteem, work and social adjustment [150]. Moreover, these improvements were sustained six months after the therapy for the 41 patients whom provided follow-up data. Patients' subjective reports of the effects of mindfulness-based stress reduction therapy are overall positive for subjects with and without epilepsy, but randomized controlled studies are needed.

Table 3
Selected clinical approaches for stress management in PWE.

	Effects on seizure reduction	Effects on comorbidities	Long lasting effect tested	Neurobiological underpinnings
Chronic stress				
Mindfulness-based therapies	Yes More than 50%	Yes Anxiety Depression Perceived-stress QOL Self-esteem	6 months in 41 patients	Neuroplasticity effect on neural circuits implicated in perception and emotional processing
Yoga	Yes About 50%	Stress Depression QOL	No data available	↑ PNS activity ↑ GABA system activity ↓ HPA-axis activity
Stress reflex				
CBT	No	Yes QOL Depression Suicidal ideation	Not maintained 3 months later in 31 patients	Neuroplasticity effect on neural circuits implicated in perception and emotional processing
GSR biofeedback	Yes About 50%	Yes Depression Negative affect	Seizures: 3 years in 2 patients Stress and comorbidities: no data available	↓ Cortical excitation

1.3.2.2.1.2. Yoga. Yoga is considered as one of the "mind-body" approaches. It includes physical postures, breathing exercises and meditation. It appears to be an effective method to cope with chronic stress by inducing relaxation. Successful yoga interventions have been reported in stress reduction and depression care [151–154]. It is hypothesized that yoga practice reduces stress responses through inducing increased parasympathetic nervous system and gamma amino-butyric acid (GABA) system activity and decreased HPA-axis activity, so that optimal homeostasis is restored [155]. This mechanism could be an explanation of the potential efficacy of yoga practice in seizure frequency and QOL in the management of refractory epilepsy. Indeed, in one study yoga practice was associated with reduction of about 50% in seizure frequency and improvement in quality of life [150]. Only a few studies have investigated the effects of yoga in the management of refractory epilepsy and its associated comorbidities. Its practice can be encouraged but in the present lack of outcomes its effectiveness remains to be fully evaluated [142].

1.3.2.2.2. Stress reflex management: cognitive-emotional based therapies
1.3.2.2.2.1. Cognitive-behavioral therapies (CBT). Cognitive-behavioral therapies (CBT) involve the examination of the relationship between thoughts and emotions linked to a stressful situation and aim to provide strategies for changing maladaptive thoughts. It is useful to cope this acute stress in immediately coping with this the cognitions and emotions associated with a stressful thought or event. In epilepsy they can target emotion regulation and depressive and anxiety symptoms or seizure control. While a certain efficacy of CBT has been shown on well-being, its effect on seizure control is less clear [142]. When CBT is designed to focus especially on depression symptoms they are possibly efficient, whereas those focusing on seizure control have shown no significant efficacy [156].

After 12 sessions of CBT focusing on epilepsy-related problems, associated psychopathology and on the development of psychological strategies to reduce seizure occurrence, six patients reported that their epilepsy-related problem had less impact on their everyday life. In addition, they report an increasing use of escape avoidance coping strategies. These effects were observed despite any decrease in seizure frequency [157]. In patients with TLE, CBT compared to SSRI shown better improvement in QOL but similar efficacy on depression. No decrease in seizure frequency was observed in any of the two groups [158]. However, these observations in small groups of patients have not been confirmed by other results. Twenty PWE received CBT treatment designed to target depression symptoms and anxiety in epilepsy for 9 sessions; although they reported improvement in depression symptoms, this was not the case for anxiety and QOL and in addition, the positive results were not maintained three months later [159].

1.3.2.2.2.2. Biofeedback. Biofeedback provides effective control strategies to regulate physiological activity. The patient learns how to control (mastery) his own physiological activity (autonomy) through a clearly perceptible feedback of this activity (perceptibility) that guides and positively reinforces effective strategies (motivation) discovered by the patient and embedded in long-term memory (learnability) [160]. This is based on monitoring a patient's bodily responses using heart rate, electrodermal activity (EDA), or brain waves; in the latter case, biofeedback using recorded EEG activity is called neurofeedback. Through visual and auditory feedback, patients learn how to voluntarily modulate their physiological responses in real time [161]. Protocols using EEG [162,163] and EDA [164] have been investigated and have shown efficacy in terms of seizure reduction, even years later according to a few small studies [165,166]. The aim of these methods is to teach patients how to voluntarily reduce cortical excitation (in neurofeedback) or increase peripheral sympathetic arousal (in EDA biofeedback) to decrease the seizure threshold [75,74]. Thus, biofeedback is a situational intervention, the strategies learned in training sessions are particularly interesting to use in prodromal situation.

In addition to a mean reduction of seizures of about 50% with a positive correlation between reduction in seizure frequency and degree of patients' improvement in EDA over biofeedback sessions [164] a positive effect on psychometric evaluation of depression and negative affect has been reported in patients with stress-triggered seizures [140]. These results suggest an additional positive effect of this method on well-being. This improvement in well-being could also be explained by an effect of increased self-efficacy and PSC since patients could learn to inhibit their seizures to some degree using their own strategies.

2. Conclusion

Depressive and anxiety disorder comorbidities and the perceived stress/self-control dimension are at the heart of the illness burden of PWE. Lack of robust data in many aspects of this domain indicates the ongoing need for systematic investigation. Many clinical health psychology tools can be useful to screen for these epilepsy comorbidities. These can reveal a more detailed picture of each patient's unique psychological makeup, which is necessarily determined by multiple and multi-scale etiological factors, including genetic and epigenetic predispositions, early life psychosocial context, occurrence of stressful life events, epilepsy type and severity, medication use, personality traits and various other elements that interact to produce a particular "stress

profile" for a given individual. This baseline stress profile will be more or less "activated" according to current life conditions, symptom burden and the dynamic balance between resilience and vulnerability. Better characterization of individual patient profiles, in terms of identifying perceived stress and coping style for example, could help in choosing appropriate therapeutic strategies with respect to each patient's areas of vulnerability and resilience, thus maximizing the chance of successful outcome. Management of stress regulation in PWE through appropriate therapeutic approaches, complementing anti-seizure treatment, can greatly improve patients' QOL and may also improve epilepsy outcome. These issues highlight the need for close collaboration between neurologists, psychiatrists and psychologists within the epilepsy field.

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