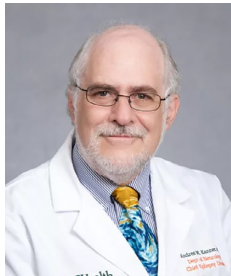**SUPPLEMENT ARTICLE**

Bidirectional relations among common psychiatric and neurologic comorbidities and epilepsy: Do they have an impact on the course of the seizure disorder?

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SUMMARY

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The treatment of epilepsy is not limited to the achievement of a seizure-free state. It must also incorporate the management of common psychiatric and neurologic comorbidities, affecting on average between 30 and 50% of patients with epilepsy, which have a significant impact on their lives at various levels, including quality of life and the prognosis of the seizure disorder. Mood and anxiety disorders are the most frequent psychiatric comorbidities, whereas stroke and migraine are among the more common neurologic comorbidities, migraine among the younger patients and stroke among the older patients. Not only do these psychiatric and neurologic comorbidities each have a bidirectional relation with epilepsy, but primary mood disorders have a bidirectional relation with these 2 neurologic disorders. Furthermore, depression and migraine have been each associated with a more severe epilepsy course, whereas depression has been associated with a more severe course of stroke and migraines. The purpose of this article is to review the clinical implications of the complex relations among epilepsy and these 3 comorbid disorders, and to identify any clinical and/or experimental evidence that may suggest that having more than one of these comorbid disorders may increase the risk of and course of epilepsy.
KEY WORDS: Stroke, Migraine, Major depressive episodes, Treatment-resistant epilepsy.

Comorbidities in epilepsy are those conditions that have a higher prevalence in people with epilepsy (PWE) than in the general population,[1] either because they are

a complication of the seizure disorder or because they share common pathogenic mechanisms, which facilitate the development of one condition in the presence of the other. Psychiatric and neurologic comorbidities are relatively frequent in PWE, affecting on average between 30 and 50% of patients and having a significant impact on their lives, including quality of life and the course and prognosis of the epilepsy and neurologic comorbidities (NCs).[2–5]

Population-based studies have identified a 35% lifetime prevalence of psychiatric comorbidities (PCs), of which mood and anxiety disorders are the most frequent in adult and pediatric populations, and attention-deficit/hyperactivity disorder (ADHD) is the most frequently recognized in children.[2] Stroke and migraines are 2 relatively common NCs in PWE, with migraine being the

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KEY POINTS

- Depression, migraine, and stroke are common comorbidities of epilepsy with a bidirectional relation among each of the entities
- Depression and migraine are associated with a worse course of the seizure disorder
- Management of psychiatric and neurologic comorbidities should be an integral part of the effective management of epilepsy

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most frequent among younger patients[3] and stroke among the elderly.[4,5] Indeed, 8–15% of PWE are reported to have migraines, whereas stroke accounts for 30–50% of epilepsy after the age of 60.[3,5] Two large population-based studies found a two- to sevenfold higher prevalence of stroke and migraine in PWE than in the general population.[5–7] Furthermore, the prevalence rates of PCs, like mood and anxiety disorders, are high among patients with primary migraine and stroke.[8]

Typically, in PWE, clinicians consider PCs to be a complication of the seizure disorder, whereas the seizure disorder is considered to be a complication of NCs (e.g., stroke). Yet, the relation between epilepsy and these PCs and NCs and the relation among PCs and NCs are complex. First, a bidirectional relation has been identified between epilepsy and several PCs, including mood and anxiety disorders, ADHD, and psychotic disorders in several population-based studies.[9–12] In addition, a bidirectional relation has also been identified between epilepsy on the one hand and migraine and stroke on the other.[10,13,14] Third, a bidirectional relation has been reported between depression on the one hand and migraine and stroke on the other.[15,16] Thus, not only are PWE at increased risk of developing these NCs and PCs, but the existence of migraine and stroke and/or primary mood, anxiety, ADHD, and psychotic disorders increases the risk of developing epilepsy.

The complex relation among epilepsy, PCs, and NCs may not only be responsible for the higher prevalence rates of PCs and NCs in PWE but may also have an impact on the course of the epilepsy and neurologic disorders. Indeed, patients with a history of depression preceding the onset of epilepsy have an increased risk of developing treatment-resistant focal epilepsy.[17–19] By the same token, a history of depression has been associated with a worse course of migraine[20] and stroke.[21] Thus, if depression is associated with a worse course of epilepsy and of these 2 NCs, does depression in patients with primary migraines and stroke increase even more their risk of developing epilepsy and its severity. The purpose of this article is to review the available literature on this question.

Complex relation between common psychiatric comorbidities and epilepsy

Bidirectional relation between mood disorders and epilepsy

Several population-based studies have suggested that primary depression increases the risk of developing epilepsy by twofold and suicidality by three- to fourfold,[9,19] and as indicated above, a mood disorder preceding the onset of epilepsy has been associated with an increased risk of developing treatment-resistant epilepsy.[17–19] It follows from these observations that treatment of PCs should be followed by an improved seizure outcome and better tolerance of antiepileptic drugs (AEDs). Yet, no data are yet available to establish whether such an association exists.

The existence of common pathogenic mechanisms operant in both epilepsy and mood disorders, has been suggested as the explanation of their bidirectional relation. This topic has been reviewed in great detail in other publications by these authors (AMK and AM) and will not be repeated here.[22,23]

Complex relation among epilepsy, mood disorders, and common neurologic comorbidities of epilepsy

Migraine and stroke are 2 common neurologic comorbidities that have a bidirectional relation with epilepsy on the one hand and with depression on the other.

Bidirectional relation between migraine and epilepsy

The onset of migraines can precede, follow, or appear simultaneously with that of epilepsy.[3,24] Furthermore, migraines can be related to the time of seizures, presenting as preictal, ictal, or postictal headaches, or can occur independently of seizures. The prevalence of epilepsy among patients with migraine (PWM) ranges from 1 to 17% (vs 0.5–1% in the general population), whereas the prevalence of migraine in PWE ranges from 8 to 15%.[3,24]

In a population-based study, PWE were found to have a 2.4-fold increased risk of migraine.[24] A retrospective population-based study estimated the adjusted hazard ratio (aHR) of developing epilepsy among 10,016 adults 20-years-old or older diagnosed with migraine between 2000 and 2009 when compared to a control cohort of 40,064. In the migraine cohort, the aHR was 1.85 (95% confidence interval [CI] 1.22–2.81). The incidence of developing epilepsy was increased in patients aged 20–44 years, yielding an aHR of 2.14 (95% CI 1.24–3.68); the aHR for developing epilepsy in female migraineurs was 2.04 (95% CI 1.20–3.48) and that of males migraineurs 1.53 (95% CI 0.78–3.00).[25]

The bidirectional relation between migraine and epilepsy was suggested in a population-based study done in Iceland that included all children age 5- through 15-years-old with newly diagnosed epilepsy or first unprovoked seizure from

December 1995 through February 1999.[14] A history of migraine was associated with a fourfold increased risk for developing epilepsy and a threefold higher risk of developing a first unprovoked seizure. Of note, migraines with auras were associated with an eightfold risk for developing first unprovoked seizures (95% CI 2.7–24.3).

Comorbid migraines have been found to have a negative impact on the prognosis of epilepsy. For example, in a follow-up study of 59 PWE with migraine and 56 without migraine, those with migraine had a significantly lower cumulative probability of being seizure-free over 10 years compared with patients without migraine (5% vs. 25%).[26] Furthermore, those patients with migraine also had a seizure disorder of longer duration, a lower early treatment response, a higher incidence of treatment-resistant epilepsy, and a lower likelihood of achieving remission with polytherapy for at least the last 2 years of follow-up.

Potential pathogenic mechanisms

Several common pathogenic mechanisms operant in both conditions have been suggested as an explanation of this bidirectional relation in a review of the literature.[27] These include genetic mechanisms involving several ion-transporter genes (*SCNA1*, *CACNA1A*, *ATP1A2*), which have also been involved in different types of epilepsy and febrile seizures; neurotransmitter disturbances affecting serotonergic, dopaminergic, and glutamatergic mechanisms; and ion-channel dysfunction (including sodium, potassium, and chloride). All of these mechanisms may yield increased cortical hyperexcitability, which is reflected by the presence of epileptiform discharges and/or of positive photoparoxysmal responses on electroencephalography (EEG) recordings of patients with migraine (in the absence of any history of clinical seizures). Furthermore, several authors have considered that the auras in migraines are the expression of an alteration in cortical excitability, mediated by cortical spreading depression, which corresponds to "a slow wave of neuronal hyperexcitability spreading at a velocity of 3–5 mm/min, followed by a depression of cortical electrical activity."[28,29] This phenomenon is associated with an increase in potassium and glutamate concentrations in the extracellular space and the intracellular entry of calcium, sodium, and chloride. Thus, does the hyperexcitable state associated with auras explain the increased risk of epilepsy in migraines with auras? This is a very attractive hypothesis, given the lack of an increased risk of epilepsy associated with migraines without auras.

The increased incidence of stroke in women with migraine may be another potential pathogenic mechanism associated with the increased risk of epilepsy in these patients.[29] Given the close relationship and shared pathogenic mechanisms between the 2 conditions, it is not surprising that several AEDs, including valproic acid and topiramate, have shown to be effective and are used widely in the prophylactic treatment of migraines and epilepsy.

Bidirectional relation between migraine and mood disorders

Epidemiologic studies have found that migraine is associated with an increased prevalence of mood disorders. For example, in a population study of 36,984 subjects from Canada, the prevalence of major depressive disorder Major depressive disorder (MDD), bipolar disorder, panic disorder, and social phobia was more than 2 times higher in patients with migraine than in those without.[30] In a case-control study of 1259 patients with recurrent major depressive episodes (MDEs) and 859 healthy controls, recurrent MDEs were associated significantly with a greater than fivefold higher prevalence of *migraine with aura*, more than a threefold higher prevalence of migraine without aura, and a twofold higher prevalence of other nonmigraine chronic headaches.[31]

Furthermore, suicide attempts have been associated with migraine with aura. In one study of 1007 young adults, those with migraine had higher rates of suicide attempts than persons without migraine, with patients with migraine with aura being at significantly higher risk of suicide (odds ratio [OR] for suicide attempts in migraine with aura: 3.0, 95% confidence interval [CI] 1.4-6.6, after adjusting for coexisting major depression and other psychiatric disorders.[32] Migraine without aura was not associated with an increase in suicide risk. These data were confirmed by data from another study of 121 adolescents with chronic daily headache, in whom migraine with aura (in contrast to patients with migraine without aura) was a predictor for suicidal risk after controlling for gender, depression, and anxiety disorders.[33]

A bidirectional relation between migraine and mood disorders was suggested in a study by Breslau et al.,[15] who found that compared to healthy controls, patients with migraine had significantly higher rates of depression after the onset of migraines, whereas patients with major depression had significantly higher rates of migraine after the onset of depression at follow-up. Of note, this bidirectional relation was identified only for migraines and not for other chronic headaches.

Common pathogenic mechanisms operant in migraines and depression

Neurotransmitter, genetic, and inflammatory disturbances have been considered as potential mechanisms operant in both migraine and depression. Among the neurotransmitters, serotonin is known to play a pivotal role in depression and suicidality and is known to play an important role in the regulation of the migraine-related pain as, high concentration of serotonin receptors have been identified in cerebral structures linked with pain regulation.[34,35] A potential common pathogenic role of dopamine in

depression and migraine has been suggested by the involvement of the dopamine D2 receptor gene in migraine with aura and MDD.[36]

Shared genetic mechanisms between migraine and depression have been proposed as a potential common pathogenic mechanism. For example, in one study of 2652 subjects participants of the Erasmus Rucphen Family genetic isolate study, 360 were found to have migraine, 209 without aura and 151 with aura. The OR for depression increased among patients with migraine but was highest among those with aura (OR 1.29, 95% CI 0.98–1.70 vs. 1.70, CI 1.28–2.24). Heritability estimates were significant for all patients with migraine but highest for those with migraine with aura.[37] In a twin study, migraine and MDD were found to share genetic factors, as an estimated 20% of the variability in depression and migraine was due to shared genetic factors, whereas 4% was due to shared unique environmental factors.[38]

Relation between migraine, depression, and epilepsy

The data cited above reveals a complex relation between all 3 conditions, with major clinical implications. First is the bidirectional relation between migraine with aura and MDD; next is the association between migraine with aura and increased suicidal risk; third, is the worse prognosis of the seizure disorder associated with migraine.

The relative impact of depression, suicidality, and migraine on the risk of developing epilepsy was investigated by Hesdorffer et al., in a population-based study carried out in Iceland, which included 324 subjects aged 10 years and older and 647 age- and gender-matched controls.[10] The highest risk for an unprovoked seizure was identified among subjects with suicide attempt + major depression (OR 7.9), compared to suicide attempt alone (OR 4.7) or migraine with aura alone (OR 2.4). Likewise, patients with major depression + migraine with aura had a higher risk of a first seizure (OR 4.6) compared to migraine with aura alone (OR 2.5) or major depression alone (OR 1.4). Furthermore, the seizure risk was higher in subjects with all 3 comorbidities (OR 6.7) compared to 2 (OR 4.9) and one condition (OR 2.0), respectively.

Clearly, this study suggests an additive effect on seizure risk in the presence of migraine with aura and major depression and/or suicide attempt. Two important questions are yet to be investigated: what is the impact of these comorbidities on the severity of the seizure disorder and what is the effect if any of successful treatment of these comorbidities on the course of the seizure disorder? Unfortunately, depression and migraines remain undertreated in the US population[39] and are infrequently addressed within the neurologic clinic, in particular in the pediatric population.[40] Not surprisingly, these 2 comorbid disorders of epilepsy have been associated with a worse quality of life in PWE.[41]

Bidirectional relation between stroke and epilepsy

There is unquestionable evidence that a history of cerebrovascular disease increases the risk of developing epilepsy.[4,42] In fact, patients with stroke have a 17-fold higher risk of developing epilepsy compared to the general population.[4] Based on these observations, it is not surprising that the relation between epilepsy and stroke is typically considered to be unidirectional. Yet, there is evidence that patients with epilepsy may have an increased risk of stroke, and thus, that stroke and epilepsy may have a bidirectional relation. For example, a population-based study conducted in the United Kingdom using data from the General Practice Research Database, compared the risk of developing a stroke between 4709 subjects who had seizures beginning at or after the age of 60 years with no prior history of cerebrovascular disease, and 4709 randomly selected controls with no history of seizures, matched for age and gender. Subjects with a history of epilepsy had a 2.89 (95% CI 2.45–3.41) relative higher hazard of developing a stroke compared with the control group.[13] Another population-based study confirmed these findings.[43] Likewise, in a prospective population-based study conducted in Finland, 245 subjects with childhood-onset epilepsy were followed at 45 years of age.[44] Of 179 surviving subjects, abnormal neurologic signs were significantly more common in subjects with uncomplicated epilepsy than in controls including a higher rate of 3T magnetic resonance imaging (MRI) abnormalities than in controls (risk ratio [RR] 2.0, CI 1.3–3.1) specifically including findings considered markers of cerebrovascular disease (RR 2.5, CI 1.04–5.9).

Yet, the higher risk of stroke in PWE may be also related to iatrogenic effects mediated by the atherogenic properties of several AEDs, primarily the first-generation AEDs, which have enzyme-inducing properties exerted through cytochrome P450 (CYP) isoenzymes. These include carbamazepine, phenobarbital, primidone, and phenytoin, and the second-generation AEDS, topiramate and oxcarbazepine, which have lower enzyme-inducing properties and which are expressed at moderately high doses.

Their atherogenic properties have been demonstrated by an increase in serum lipids including total cholesterol, low-density lipoprotein cholesterol, and triglycerides as well as increase in homocysteine and C-reactive protein (CRP).[45] Of note, although valproic acid is a CYP enzyme inhibitor, it has been associated with an increase in serum triglyceride levels. In addition, thicker intima have been identified in patients treated with these AEDs. Conversely, discontinuation and/or switch from either phenytoin or carbamazepine to AEDs with no enzyme-inducing properties (e.g., lamotrigine or levetiracetam) resulted in a significant reduction of several atherogenic chemicals including total cholesterol, low-density lipoprotein cholesterol, triglycerides, and CRP.[46] In addition, PWE in whom carbamazepine was discontinued were found to have a drop in lipoprotein levels, whereas those taken off phenytoin had a decrease in

homocysteine blood levels. In addition, oxcarbazepine and topiramate, at doses >200 mg and 900 mg/day, respectively, have been associated with high homocysteinemia.[47] In addition, there is a question whether the atherogenic properties are limited to enzyme-inducing AEDs, as a more recent study identified an association between AEDs without enzyme-inducing properties and an increase in several atherogenic chemicals.[48] Thus, we can hypothesize that in patients at risk of vascular disease, exposure to AEDs, in particular those with enzyme-inducing properties, can increase the risk of developing a stroke.

Bidirectional relation between stroke and depression

Several cross-sectional studies have identified prevalence rates of poststroke depression (PSD) ranging from 30 to 50%.[49] In a review of the literature, for example, of population-based studies, the prevalence rate of all types of depression was estimated at around 31.8% (range 30–44%).[49]

Conversely, the increased risk of stroke associated with a prior history of depression was investigated in one meta-analyses, which included data from 28 prospective cohort studies that encompassed 317,540 subjects among whom 8478 stroke cases were identified during a follow-up period ranging from 2 to 29 years.[16] The investigators found that a history of depression was associated prospectively with a significantly increased risk of developing a stroke, as the pooled aHRs for total stroke were 1.45 (95% CI 1.29–1.63), 1.55 for fatal stroke, (95% CI 1.25–1.93), and 1.25 for ischemic stroke (95% CI 1.11–1.40).

A worse course of the stroke in the presence of PSD may be another consequence of the bidirectional relation between these 2 conditions. For example, the presence of PSD has been associated with a worse recovery of cognitive impairment and impairment of activities of daily living. These data were reviewed in great detail elsewhere and will not be repeated here.[49]

Pathogenic mechanisms

The potential pathogenic mechanisms operant in depression that can contribute to the development and/or worsening of vascular disease include a hyperactive hypothalamic-pituitary-adrenal axis, (HPA-A) which can facilitate the development of cardiac arrhythmias and a hypercoagulable state and immunologic disturbances leading to microvascular inflammation.

An HPA-A was the first biologic biomarker identified in MDDs in humans and has been demonstrated as well in animal models of depression (see below). The resulting elevation of serum cortisol has been associated with an increased risk of atherosclerosis and sympathoadrenal hyperactivity, which in-turn can lead to vasoconstriction, platelet activation, and an elevated heart rate.[50] In addition, an increased sympathetic or decreased parasympathetic activities have been associated with a decreased heart rate variability,

yielding in-turn to a higher risk of cardiac arrhythmias and sudden death.[51–54]

The sympathoadrenal hyperactivity and the HPA-A can facilitate a *hypercoagulable state* through an elevation of factor VIII and von Willebrand factor, whereas catecholamines can lead to an increase in fibrinolysis.[55] In addition, abnormal platelet function manifested by an increased platelet reactivity (by up to 40%) has been reported in untreated patients with depression,[56] mediated by abnormal platelet serotonin receptors[35,57], which can be reversed with selective serotonin reuptake inhibitors (SSRIs).[58–60]

In addition, increased cytokine levels, including interleukin (IL)-1β, IL-6, and tumor necrosis factor α have been associated with depression, which in-turn can result in microvascular inflammatory processes and increase the risk of stroke.[61]

Relation between depression, epilepsy, and stroke

Given the bidirectional relations between depression and epilepsy and stroke and epilepsy, patients with stroke and depression should be expected to be at increased risk of developing epilepsy compared to patients with only stroke or only depression. Furthermore, the seizure disorder would be expected to be more likely to be refractory to pharmacotherapy. Yet, a review of the literature identified only one study that was indirectly related to these questions. This was a population-based study from Taiwan, which investigated whether the use of SSRIs increased the risk of developing epilepsy[25] and in which a total of 4688 subjects were enrolled; those exposed to an SSRI had 2.45-fold higher risk of developing epilepsy than those who did not receive antidepressant drugs, and the investigators attributed their findings to the use of SSRIs. An editorial in the same issue of the journal in which the study was published cautioned the readers on the conclusions reached by the Taiwanese investigators, as they had failed to factor-in the role of the depressive disorder for which the SSRIs were prescribed in the higher risk of epilepsy.[62] In fact, the increased risk of epilepsy identified in this study was comparable to a 2.5 higher risk reported in 2 population-based studies from the United Kingdom cited earlier.[9,19]

A potential proconvulsant effect of antidepressant drugs has been a source of confusion among clinicians and remains one of the causes of undertreatment of mood and anxiety disorders in PWE. Therefore, misinterpretation of the data as evidenced in the Taiwanese study can result in extremely detrimental effects, causing clinicians to refrain from providing pharmacotherapy to PWE with depression.

In fact, the available evidence suggests that, with certain exceptions, antidepressant drugs *do not* have proconvulsant properties *when used at therapeutic doses*. For example, in a study by Alper et al., the incidence of epileptic seizures in patients with a primary psychiatric disorder was compared with those that were randomized to a psychotropic drug and to placebo in the course of phase II and III, multicenter

randomized-placebo controlled trials.[63] Data from a total of 75,873 patients with primary mood, anxiety, and psychotic disorders were included from trials that had been submitted to the US Food and Drug Administration (FDA) for regulatory purposes between 1985 and 2004. In addition, the investigators compared the seizure incidence during the randomized-placebo-controlled trials with that of the published rates of unprovoked seizures in the general population. Among the antidepressant drugs, the data included trials with several tricyclic antidepressants (TCAs), SSRIs, the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine, the α2-antagonist mirtazapine, and the norepinephrine-dopamine reuptake inhibitor bupropion. The incidence of seizures was significantly *lower* among subjects randomized to antidepressants compared to those given placebo (standardized incidence ratio 0.48, 95% CI 0.36–0.61), whereas in subjects randomized to placebo, seizure occurrence was 19-fold *higher* than that expected in the general population. Of note, in both patients assigned to antidepressants and placebo, the seizure incidence was greater than the published incidence of unprovoked seizures in the general population. A higher incidence of seizures was found among patients randomized to 2 antidepressant drugs, bupropion and clomipramine, than in those randomized to placebo. In a separate study, the antidepressant maprotiline was reported to increase the risk of seizures in patients without epilepsy in a dose-dependent manner.[64]

There is a general consensus that antidepressant drugs can cause seizures at toxic doses and, in fact, most reported seizures associated with antidepressants have occurred in the case of overdoses. These observations are supported by data from an experimental study done in rats in which spontaneous temporal lobe seizures were induced following hippocampal administration of pilocarpine.[65] Seizure prevention was observed when intrahippocampal perfusion of serotonin yielded extracellular concentrations ranging between 80 and 350% of baseline serotonin levels, while worsening of seizures occurred at concentrations >900% of baseline, a phenomenon mediated through glutamatergic mechanisms.

The data of the study of Alper et al. support the increased risk that patients with primary depression have of developing unprovoked seizures and epilepsy alluded to above, but also raises the question of whether SSRIs and SNRIs may yield a protective antiepileptic effect. As discussed below, data from several experimental studies in animal models of epilepsy may suggest an antiepileptic effect of SSRIs and TCAs, although some studies have suggested the opposite findings. Unfortunately, there are no data from controlled trials in PWE as of today, but 5 open trials conducted in PWE have suggested a possible antiepileptic effect. In one study, for example, investigators compared the frequency of seizures during the 6 months preceding the start of an SSRI or SNRI with that recorded during the 6 months on the psychotropic drug.[66] Among the 84 patients included, 44 were

experiencing more than one seizure/month before the start of antidepressant; 27.5% of these patients went on to have fewer than one seizure per month on the psychotropic drugs. Furthermore, none of the 40 patients with fewer than one seizure per month went on to have more than one seizure per month. Of note improvement in seizure frequency was independent of remission of psychiatric symptoms.

In summary, there are no available clinical data to establish whether the comorbid occurrence of stroke and depression can worsen the risk and/or the severity of epilepsy.

Can animal models of depression, epilepsy, stroke, and migraine demonstrate an agonistic effect of these 3 comorbidities on the development and course of epilepsy?

Can a bidirectional relation between depression and epilepsy be identified in animal models of epilepsy?

In previous publications, we hypothesized the existence of common pathogenic mechanisms operant in PC and epilepsy as an explanation of the bidirectional relation between epilepsy and these psychiatric disorders.[13,14]

Psychiatric phenomena facilitate epileptogenesis: Several experimental studies conducted in rodents have demonstrated that chronic stress induced by maternal separation, prolonged physical restraint, cold stress, and sleep deprivation leads to the development of depressive behaviors, as evidenced by increased immobility in the forced swimming test (FST) in rats and in the tail suspension test in mice (which serve as indicators of hopelessness/despair), as well as the loss of saccharin or sucrose consumption preference (which suggests the presence of anhedonia).[67,68] These phenomena has been associated with HPA-A hyperactivity,[69–71] demonstrated by the elevated plasma corticosterone level and/or positive dexamethasone (DEX) or DEX/Corticotropin-releasing hormone tests.[72] Furthermore, mice that are bred selectively to display this depressive phenotype have chronically elevated plasma corticosterone levels.[73]

At the same time, hyperactive HPA-A resulting from either stress or exogenously applied corticosterone, primes the brain for epilepsy. Thus, repeated physical restraint in rats accelerates the rate of amygdala kindling (i.e., reduces the number of electrical stimuli needed to reach fully kindled state) and increases the duration of secondary generalized complex partial seizures.[74] Repeated separation of neonatal rat pups from dams also accelerates the rate of amygdala kindling,[75] increases the sensitivity to pentylenetetrazole-induced convulsions in adulthood, and exacerbates the increase of plasma corticosterone levels under conditions of pilocarpine status epilepticus.[76]

Conversely, depressive-like impairments have been well established in animal models of temporal lobe epilepsy (TLE). Thus, kindling of limbic seizures,[77–79] status epilepticus (SE) induced by pilocarpine[80] and kainic acid,[81] produced persistent interictal behavioral (e.g., anhedonia and

despair/hopelessness[77,80,81]), neuroendocrine (e.g., the dysregulation of the HPA axis[81,82]), neurochemical (e.g., suppressed monoaminergic, especially serotonergic, tone in depression-relevant pathways[80,83]), and receptor (e.g., upregulation of serotonin type 1A (5-HT1A) autoreceptors and downregulation of 5-HT1A terminal receptors[84]) perturbations indicative of depressive disorder.

The analysis of available data suggests that chronic, persistently increased seizure susceptibility is more closely connected to depressive-like abnormalities than to recurrent seizures themselves. For example, in a typical kindling paradigm, seizures develop in response to repetitive mild electrical stimulations of a limbic structure; the "kindling state" is characterized by the permanently increased propensity/decreased threshold to seizures, but not by spontaneous seizures *per se*.[85] Nevertheless, kindled animals consistently develop depressive-like impairments, such as despair/hopelessness and anhedonia, and these impairments are present long after the last seizure is induced.[77] Instead, the severity of depressive behaviors correlates positively with the increased neuronal excitability, evident as the decreased threshold and/or increased duration of focal afterdischarge induced from kindled sites (e.g., hippocampus, amygdala).

Status epilepticus produces chronic epilepsy more resembling human TLE than kindling, whereby the animals develop spontaneous recurrent seizures.[86,87] In post-SE models, the animals present with the spectrum of behavioral, neuroendocrine, neurochemical, and receptor impairments indicative of a depressive state.[79,80] However, several studies examining the relation between the severity of post-SE epilepsy and depression, failed to find a correlation between the 2. Instead, similar to kindling, interictally increased neuronal excitability (analyzed by gauging afterdischarge properties) showed strong correlation with the severity of depressive impairments.[79]

In addition to correlation analysis, some inference can be made from the observed effects of antidepressant drugs on experimental epilepsy. Most experimental studies have shown that SSRIs,[79,88–91] native serotonin molecule,[92] and norepinephrine reuptake inhibitors (NERIs)[88,93] exert antiepileptic effects in animal models of TLE, including kindling, pilocarpine, and kainic acid models.

Can a bidirectional relation between migraine and epilepsy be identified in animal models of epilepsy?

The development of equivalent symptoms of depression and anxiety in a rat model of migraine were demonstrated in one study, which used a chronic migraine model based on the method of repeated dura mater inflammatory soup infusion.[94] Development of equivalent symptoms of depression and anxiety were compared between rats subjected to the inflammatory infusion cocktail and control rats; symptoms of depression were assessed with the sucrose preference test, whereas the open field and elevated plus maze tests were used to identify equivalent symptoms of anxiety. The

study rat group displayed symptoms of both depression (a decrease in the sucrose preference) and anxiety (suppressed locomotion and rearing in the inner quadrants of the open field, and decreased presence in the open arms of the elevated plus maze). Furthermore, significantly lower serotonin and dopamine levels were detected in the prefrontal cortex of the study rat group compared with those of the control group; the neurotransmitter imbalance was reversed by low-dose of amitriptyline.

Of note, patients with migraine and depression are known to have a persistent decrease in serotonin levels. Furthermore, the low dopamine cortical concentrations demonstrated in this animal model of migraine is supported by previous reports of low dopamine levels in patients with migraine, in whom a D2 receptor genotype has been related to the comorbidity of migraine and depression.[36]

Can a bidirectional relation between migraine and epilepsy be identified in animal models of epilepsy?

A review of the literature failed to identify any experimental study that investigated this question.

Clinical implications and consideration of future research

In this article we review the very complex relation among epilepsy and 3 of its more common neurologic and psychiatric comorbidities—stroke, migraine, and depression—as well as the potential clinical implications of such relations. We selected these comorbidities not only because of their high comorbid occurrence in PWE, but because of their bidirectional relation among each comorbidity and between their respective bidirectional relations with epilepsy.

Although an increased epilepsy risk is associated with each of the 3 comorbidities individually, available data for an additive risk could be identified only for the comorbid occurrence of depression and migraine,[10] but not for stroke and depression. A history of depression and migraine has been associated with an increased risk of treatment-resistant epilepsy, individually, the combined impact of the 2 comorbidities occurring together on the course of the seizure disorder has yet to be established. Neither has the effect of a successful treatment of each comorbidity on the severity of the epilepsy been investigated and vice versa. Clearly, these questions need to be investigated in future prospective studies.

Failure to recognize bidirectional relations among epilepsy and these 3 common comorbidities may result in misinterpretation of results with negative clinical implications. For example, the Taiwanese study cited above[25] illustrates the consequences of failing to factor-in the impact of the bidirectional relation between mood disorders and epilepsy on the interpretation of the role played by SSRIs on the development of poststroke seizures. Indeed, clinicians reading that study may be left with the impression that this class

of antidepressant drugs increases the risk of developing epileptic seizures in patients who had a stroke. Clearly, such conclusions can have grave consequences for the pharmacologic treatment of depression not only in any PWE but also in any patient with neurologic disorders associated with an increased risk of epilepsy, such as stroke, traumatic brain injury, Alzheimer's dementia, and brain tumors.

Today, identification of biomarkers of the epileptogenic process has taken front and center in epilepsy research. Although clinical and experimental data appear to suggest that depression is associated with an increased risk of epilepsy, its role as a potential biomarker of the epileptogenic process, if at all, is yet to be established and the increased epilepsy risk may result from the existence of common pathogenic mechanisms operant in both conditions. The same observations can be made for the other 2 comorbidities of epilepsy discussed in this article. Experimental studies are needed to address this question. For example, the number of stimulations necessary to achieve the full kindling state can be compared among 2 groups of rats: (1) control rats, undergoing a kindling process; and (2) rats initially subjected to interventions geared to trigger the equivalent of a depression and then subjected to the development of migraine equivalent. The same paradigm can be followed in testing any additive effect of depression on stroke on the epileptogenic process. This type of experimental model can also be applied in other neurologic conditions associated with epilepsy, such as dementia and traumatic brain injury.

In summary, the treatment of epilepsy cannot be limited to the achievement of a seizure-free state via pharmacologic and/or surgical therapies. It must incorporate a thorough understanding of the complex relations among common neurologic and psychiatric comorbidities, which often play a role in the course and treatment of the seizure disorder.[95]

DISCLOSURES

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