Depression in epilepsy: a critical review from a clinical perspective

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Abstract | Depression is a serious and frequent comorbidity of epilepsy and other neurological conditions. Here, we review recent studies on the relationship between epilepsy and depression with regard to diagnostic criteria, epidemiology, etiology and treatment. Depression in epilepsy can be described in the general framework of the diathesis–stress model: chronic stress exposure owing to the 'burden of epilepsy' and learned helplessness due to the threat of recurrent seizures as unpredictable aversive events represent psychological risk factors for the development of depression. Epilepsy-related factors (for example, focus site or side) have shown little effect on mood. Nonepileptic individuals who are adversely affected by seizures (for example, parents of pediatric patients with epilepsy, and patients with psychogenic nonepileptic seizures) show increased levels of depression, similar to patients with epilepsy. However, seizures, subclinical hypersynchronous neural discharges and some antiepileptic drugs may cause acute states of depressive mood or depression on a purely neurobiological basis. Antidepressant drugs and psychotherapy have shown moderate efficacy in the treatment of depression comorbidity, but randomized controlled trials in patients with epilepsy are lacking, especially for drugs.

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Introduction

The growing impact of depression on public health is now fully recognized.[1] In chronic conditions such as epilepsy, depression comorbidity is the main cause of low health-related quality of life (HRQOL)[2–4] and doubles the overall costs of medical care.[5]

Neuropsychiatric evaluation of patients with epilepsy and other neurological disorders has received considerable attention during the past decade.[6] In 2008, a consensus statement on depression in epilepsy provided a comprehensive summary of the state of the art at that time.[7] In the same year, further thorough reviews were published on depression in epilepsy,[8,9] psychotropic adverse effects of antiepileptic drugs (AEDs),[10] the global burden of epilepsy,[11] and suicidality in epilepsy.[12,13]

Building on this broad foundation, we examine the relationship between epilepsy and depression with regard to diagnostic criteria, epidemiology, etiology and treatment. Within the scope of this clinically oriented Review, we do not address anxiety as one of the most frequent comorbidities of both epilepsy and depression,[14,15] nor do we include animal studies or other basic research.[16]

Diagnosing depression

Transient states of depressive mood commonly occur in the general population but do not usually require psychiatric support. In addition, morbidity may be accompanied by a state of feeling unwell,[17] which resembles many characteristics of depression, such as anhedonia, anergia and social withdrawal. Consequently, the evaluation of mood states must be strictly distinguished from diagnosing depression as a psychiatric disorder.

Measuring depressed mood

Self-report questionnaires are widely used in research on depression in epilepsy (Table 1). Mood strongly correlates with HRQOL, exceeding the impact of epilepsy-related factors (for example, seizure frequency) on HRQOL many times over.[2,18,19] In patients with epilepsy, subsyndromic depressed mood states (which do not fulfill the diagnostic criteria for a depressive disorder) and major depression have an equally negative impact on HRQOL.[2] Furthermore, mood is a more accurate predictor of self-reported cognitive dysfunction than are objective neuropsychological deficits.[20,21] Importantly, hopelessness seems to be a better predictor of suicidality than depressive mood.[22,23] However, altered mood is a necessary but not a sufficient condition for diagnosing depression as a mood disorder.[24] Accordingly, psychometric scales are suitable for conducting neurocognitive research on mood, but most are inappropriate for neuropsychiatric studies on mood disorders.

Diagnostic criteria

To support a psychiatric diagnosis, the presented mood state must seem in some way inappropriate or disconnected from the current life conditions and/or the personality of the patient. The key feature of clinical depression is not the state of altered mood *per se*, but the acute dysfunction of mood regulation (which is most

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obvious in bipolar disorder). Diagnosis of depression requires an individual evaluation by a board-certified psychiatrist or clinical psychologist, based on established diagnostic criteria. When defining depression, the international diagnostic systems (International Classification of Diseases, 10th Edition [ICD-10], and Diagnostic and Statistical Manual of Mental Disorders, 4th Edition [DSM-IV]) refer to a change of mood and to a loss of pleasure that interferes with normal functioning.

The neuropsychiatric evaluation of depressed patients with epilepsy must take into account seizure-related effects on mood and affect regulation, the diversity of depressive disorders, and the frequently associated psychiatric comorbidities of depression (for example, anxiety and drug abuse). In this regard, the recommendation of the International League Against Epilepsy's Commission on the Psychobiology of Epilepsy (now the Commission on Neuropsychobiology) to "ignore the presence of epilepsy in making the [psychiatric] diagnosis"[25] is disputable.

Depression is now widely accepted as a comorbidity of epilepsy,[7] which implies the existence of a concomitant psychiatric disorder.[26] For some authors, however, depression represents a psychiatric symptom of the epilepsy spectrum disorder.[27] The complex epidemiological, etiological and therapeutic relationships between epilepsy and depression require further clarification.[8,26]

Epidemiology

Epidemiological data on depression in epilepsy vary depending on diagnostic criteria, applied measures, surveyed populations and time frames. The lowest prevalence rates have been obtained in large epidemiological studies. For example, in the Canadian Community Health Survey cycle 1.1 ($n = 130,888$), the prevalence of current depression (measured according to the Composite International Diagnostic Interview, short form) was 13.0% in patients with epilepsy, compared with 7.2% for the general population (odds ratio 1.43, 95% CI 1.13–1.82).[28] Similarly low prevalence rates (below 20%) were observed in other large community-based studies.[29–31] Community-based studies on smaller samples revealed slightly higher prevalence rates of 22.0–27.6% for depression in patients with epilepsy.[32,33] Prevalence rates below 30% were also reported for presurgical[34], consecutive[35,36] and adolescent[37] patients with epilepsy. The highest prevalence rates of depression as a comorbidity of epilepsy (almost 50%)[19] are obtained in tertiary-care samples of patients, probably owing to a selection bias as these patients are most severely affected by active epilepsy; furthermore, they undergo the most comprehensive diagnostic work-up (Berkson bias).[38]

Patients with epilepsy show a similar prevalence of bipolar disorder to the general population (less than 2%).[39] Some studies of patients with epilepsy report the—obviously higher— lifetime prevalence of depression or any psychiatric disorder (58%),[40] which may be misleading if these data are confused with the prevalence rates of current depression. Patients with epilepsy have shown an increased risk of suicide (up to 10-fold)

Key points

- Depression is a frequent comorbidity of epilepsy
- Depression comorbidity in epilepsy can be explained in the framework of the diathesis–stress model
- Seizures, subclinical hypersynchronous neural discharges and some antiepileptic drugs may cause acute states of depressive mood on a purely neurobiological basis
- Nonepileptic individuals who are adversely affected by seizures (for example, parents of pediatric patients, and patients with psychogenic seizures) show elevated levels of depression, similar to patients with epilepsy
- Antidepressants and psychotherapy seem to have a comparable, moderate antidepressant effect, but randomized controlled trials are lacking, particularly for drugs
- More-comprehensive approaches to the understanding and treatment of depression and suicidality in epilepsy, which combine drug treatment with psychotherapy and rehabilitative care, need to be developed

Table 1 | Use of psychiatric classification systems and measures

Classification or measure	Number of studies	Proportion of studies (%)*
Classification		
DSM or ICD (total)	83	46.6
DSM-IV	70	39.3
ICD-10	15	8.4
ICD-9	5	2.8
DSM-III	4	2.2
Psychiatric interviews		
Neuropsychiatric assessment (total)	60	34.7
Structured Clinical Interview for DSM-IV Axis I Disorders	18	10.5
Austin Comprehensive Epilepsy Program	5	2.9
Composite International Diagnostic Interview	3	1.8
Questionnaires or ratings‡		
BDI (total: BDI, modified BDI, BDI-II)	46	26.9
BDI-II	18	10.5
Quality of Life in Epilepsy Inventory (total)	31	18.1
Quality of Life in Epilepsy Inventory-31	18	10.5
Hospital Anxiety and Depression Scale	20	11.7
Mini-International Neuropsychiatric Interview	13	7.6
Centre for Epidemiologic Studies—Depression	10	5.8
Children's Depression Inventory	10	5.8
Hamilton Depression Rating Scale	9	5.3
Child Behavior Checklist	9	5.3
Neurological Disorders Depression Inventory for Epilepsy	7	4.1
Symptom Checklist 90-item, Revised	6	3.5
Minnesota Multiphasic Personality Inventory	5	2.9
Montgomery–Åsberg Depression Rating Scale	4	2.3
Patient Health Questionnaire 9-item version	4	2.3
Profile of Mood States	4	2.3

The figures relate to empirical studies conducted in 2008–2010. Nearly one-half of the studies (46.0%) applied only one measure to assess depression and one-third (31.1%) applied two measures. *Proportions are relative to the total number of studies in which the measure could have been used. ‡Only measures that were used in more than two studies. Abbreviations: BDI, Beck Depression Inventory; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases.

Box 1 | The diathesis–stress model

The idea that a specific, intrinsic diathesis (that is, disposition or tendency) distinguishes people who develop mental disorders from those who do not was proposed as early as the 19th century (for example, by G. M. Beard). The role of extrinsic stressful life events in the onset of psychiatric disorders had also been acknowledged by that time (for example, by J. Hawkes). The two factors were first combined in the field of schizophrenia research in the 1960s (for example, by M. Bleuler, P. E. Meehl and D. Rosenthal) to explain why some individuals develop psychopathological disorders after exposure to stressful life events whereas others prove resilient to the same or higher levels of stress. The dual-factor model regarded mental disorders as the result of an interaction between objective life events (stress) and a biological (for example, genetic) predisposition (diathesis), which defines the impact of stress on the organ systems.[196] The difficulty of measuring diathesis and stress independently and objectively is now recognized. The evaluation of a given situation as challenging, overloading or threatening obviously depends on the available biological, psychological and social coping resources of an individual. Moreover, stress is now interpreted as the psychophysiological response to a demanding life event, in which integrative body systems such as the brain maintain the functional homeostasis of the organism. The cumulative amount of activation of the stress response systems during life is termed the allostatic load to the organism (that is, the threat to homeostasis).[61,62] Patients with epilepsy and nonepileptic individuals who are adversely affected by seizures are exposed to higher allostatic load, the psychological effect of which will depend on the intrinsic diathesis of the individual.

compared with the general population.[13,41,42] A high lifetime prevalence of suicidal thoughts (36.7%), plans (18.2%) and attempts (12.1%) has been reported in adult patients with epilepsy.[43]

Patients with Parkinson disease and stroke showed higher prevalence of current depression than did patients with epilepsy (19%, 16% and 15%, respectively).[44,45] Also, the interictal dysphoric disorder in epilepsy—which refers to labile depressive, labile affective and specific symptoms (for example, irritability) occurring apart from seizures[46]—is not specific to epilepsy: patients with migraine show the same prevalence of this disorder.[47]

Recent epidemiological studies confirmed that depression may antedate and increase the risk of epilepsy onset.[48,49] The evidence is not conclusive,[50,51] however, and reciprocal causal relationships with depression were also shown for cardiovascular disease,[52] diabetes,[53] Parkinson disease,[54] stroke[55] and dementia.[56]

Etiology

In 1980, the classical psychopathological distinction between endogenous and 'reactive' types of depression was omitted from the third edition of the DSM (DSM-III) in an attempt to separate objective symptoms from supposed etiologies. Nevertheless, weighing the impact of psychological and neurobiological etiological factors remains essential, especially with regard to causal therapy approaches.

Depression in epilepsy can broadly be explained in the framework of the diathesis–stress model, which provides a generic and integrative view of neurobiological and psychological factors that underlie the development of mental disorders (Box 1). According to this model, the impact of stressful life events on mental health is determined by the vulnerability of an individual. However, epilepsy can also lead to the development of acute states of depressed mood on a purely neurobiological basis.

Psychological factors

Depression in patients with epilepsy corresponds paradigmatically to learned helplessness and chronic stress exposure, which are the key concepts in psychoetiological models of depression. Importantly, these factors also affect parents of pediatric patients with epilepsy and patients with psychogenic nonepileptic seizures (PNES), who show similarly increased levels of depression to epileptic patients in the absence of epilepsy-specific neurobiological correlates.

Learned helplessness

Exposure to recurrent seizures as unpredictable, uncontrollable, and highly aversive or even life-threatening events recapitulates the experimental paradigm for inducing learned helplessness (proposed by M. Seligman in 1967), which remains the most influential behavioral model of depression.[57,58] Subsequently, cognitive psychology developed the concept of the locus of control, which describes how an individual attributes the course of life to controllable (for example, personal abilities) or uncontrollable (for example, fate) factors. Consistent with the notion of learned helplessness, patients with epilepsy showed a reduced belief in personal control regarding health compared with their peers.[59,60]

Burden of epilepsy

The burden of epilepsy represents a state of chronically increased stress and allostatic load according to the diathesis–stress model.[61,62] The burden of epilepsy is defined by underreported seizure-related injuries;[63] postictal and interictal fatigue;[64] somatic or psychiatric comorbidities; cognitive impairments; lower academic achievement; lower self-esteem; and lower socioeconomic and marital status.[65–67] Psychological distress,[68] fatigue[64] and insomnia[69] strongly contribute to depressive mood. The prevalence of critically high levels of psychological distress is doubled in patients with epilepsy compared with healthy controls.[70] In contrast to many other neurological conditions, social stigma and public ignorance represent a specific additional burden of epilepsy.[71,72] If stress-related factors are taken into account, epilepsy-related medical factors show no further effect on mood in most studies.

Burden of normality

De novo depression after epilepsy surgery occurs in less than 10% of patients and seems to be independent of the seizure outcome.[73,74] Postictal recovery from epilepsy can place the patient under considerable pressure to adjust to altered life conditions, which might result in depression. This seemingly paradoxical psychological mechanism is termed the 'burden of normality'.[75]

Resilience

Social support, family resources and higher income were shown to be protective factors against depression

in epilepsy.[76,77] Resilience is defined by a high HRQOL despite adverse conditions such as uncontrollable seizures and low socioeconomic status.[78] Resilience was associated with reduced depression, fewer worries, higher self-mastery, less feeling of stigma, improved cognition, fewer AED-associated adverse events, and better HRQOL at epilepsy onset.[78]

Seizures affect mood in nonepileptics

Depression in neurologically healthy parents of children with epilepsy provides a model for the impact of seizures on mood in the absence of epilepsy-related neuropathology. The reported rates of parental depression (12–49%)[79–82] depended partly on the severity of the pediatric epilepsy syndrome. Parental depression is related more to behavioral adjustment problems and lower HRQOL of the affected children than to epilepsy-related factors.[79,80,83,84] Young age of the child, family dysfunction, fewer family resources, increased family demands, and maternal learned helplessness are additional risk factors for maternal depression.[82,85] In one study, parents of children with epilepsy or asthma showed similarly increased rates of depression (16.3% and 18.5%, respectively) compared with parents of healthy children.[83]

PNES are defined by a lack of epileptiform neural discharges during seizures and absence of other epilepsy-related neuropathological indicators. However, patients with PNES have shown an equal or higher prevalence of lifetime and current psychopathology (especially depression) as patients with epilepsy.[86,87] The allostatic load in these patients seems particularly high; for example, male patients with PNES were three times more likely to report physical abuse in childhood (91%) than were men with epilepsy (30%).[88]

Neurobiological factors

Epilepsy provides intriguing examples of the development of depression on a purely neurobiological basis. Seizures, subclinical paroxysmal neural discharges and some AEDs may cause acute states of depressed mood. Irrespective of such acute effects, however, epilepsy-related factors generally show little effect on mood and depressive disorders, and the findings from neuroimaging studies are not conclusive with regard to the etiology of depression.

Seizures

States of depressed mood often precede[89] or follow[90] seizures. Postictal depression may last for hours or even days. Postictal manic episodes may also occur,[91] and one case report documented a postictal suicidal urge.[92] Of note, the preceding ictal events might go unrecognized (for example, nocturnal seizures),[93] so the incidence of postictal depression could be underestimated. AEDs are probably more effective than antidepressants for controlling postictal affective disorders,[90] although positive effects have also been reported for tricyclic antidepressants.[94] A study examining interictal dysphoric disorder in epilepsy found that symptoms were actually related to seizures in more than half of the patients.[24] In the majority of patients fulfilling the DSM-IV criteria for bipolar disorder, symptoms were found to be peri-ictal on closer examination.[39] Interictal depression may actually be seizure-related in many patients with active epilepsies.[95] We are not aware of any studies correlating interictal mood states with interictal epileptiform activity as measured by EEG.

Consistent with these findings, complete recovery from epilepsy[96] or complete seizure control has been shown to reduce the risk of depression, irrespective of the type of treatment (surgery or AEDs).[19,34,97–99] In addition, presurgical depression is a predictor of the postsurgical mood state.[75] However, only a minority of studies have reported a correlation between seizure frequency and depression in active epilepsies.[100,101] Reducing seizure frequency without achieving complete seizure control, therefore, probably has little effect on depressive mood. Of note, failure of epilepsy surgery may induce a state of hopelessness ('last exit closed') and has been shown to correlate with increased suicide rates.[102]

The relationship between seizures and depression seems to be reciprocal to some extent. A history of psychiatric disorders and depression has a small but significant negative effect on seizure outcome after epilepsy surgery[103,104] and on the response to AED treatment modification.[105] However, one study reported that anxiety and personality disorders, but not depression, predicted the effect of epilepsy surgery on seizures.[106] Therefore, presurgical psychiatric symptoms should be regarded as a 'red flag' for a particularly careful evaluation of the patient, but not as an exclusion criterion.

Hypersynchronous neural discharges

Paroxysmal hypersynchronous neural discharges (that is, epileptiform discharges) are the hallmark of epileptic seizures. However, neural hypersynchronicity might occur at a subthreshold level that does not produce the typical positive signs of a clinical seizure. For example, periodical lateralized epileptiform discharges (PLEDs) can cause acute catastrophic depression and other negative ictal symptoms in the absence of overt seizures.[107] On closer examination, PLEDs were found to occur in approximately 10% of patients with partial seizures.

Similarly, depression and acute unstable depressive syndrome—which is defined by brief episodes of acute depression that are often accompanied by other fluctuating psychiatric symptoms—in patients without epilepsy correlated with epileptiform EEG deviations or a history of seizures and/or epilepsy.[108–110] Of note, pathophysiological electrical activity in deep brain regions (such as the limbic region) may not be detected by surface EEG, but PET studies have suggested regional hypermetabolism.[107]

Antiepileptic drugs

Some AEDs may facilitate the development of or even cause depressive disorders.[111,112] Moreover, several studies have related AEDs to suicidality,[113–115] which resulted in a highly debated FDA black box warning for all AEDs in 2008.[116,117]

Ketter *et al.*[118] proposed a model that divides AEDs into two classes: drugs that potentiate γ-aminobutyric acid-

Box 2 | Psychotherapy for depression in epilepsy

For patients who have depression but not a neurological disease, antidepressant drug treatment combined with cognitive behavioral therapy (CBT) is an established therapeutic approach. However, depression comorbidity in patients with neurological disorders is commonly attributed a neurobiological etiology. On a background of the still-influential model of mind–brain dualism, this view seems to imply that psychotherapeutic treatments are not useful for addressing depression in this context. For example, the German 'Guidelines for the treatment of the first epileptic seizure and epilepsy in adults' (2008) recommends selective serotonin reuptake inhibitors (and mentions vagus nerve stimulation) for the treatment of depression comorbidity, but psychotherapeutic treatments are neither recommended nor discussed despite evidence of their moderate efficacy.[197]

Psychotherapy has the potential to support patients suffering from a chronic condition such as epilepsy, as it aims not only at the acquisition of behavioral, cognitive and social skills for improving life and behavior, but also at improved adaptation to given life conditions as far as they are unchangeable. CBT integrates concepts from behaviorism and cognitive psychology, and currently represents the mainstream of clinical psychology. Acceptance and commitment therapy (ACT) is a recent derivative of CBT. Like other novel approaches, ACT applies mindfulness (that is, conscious experience of the present) and shifts the therapeutic focus from reasoning to committed action. Behavioral activation is derived from CBT and has proved equally effective for the treatment of depression.[154] In this form of therapy, the patient is motivated to schedule and perform enjoyable and engaging activities on a daily basis despite the inner resistance, withdrawal tendency and anergia caused by depression. Non-cognitive approaches such as behavioral activation seem to be especially appropriate for the treatment of patients with cognitive impairment. The psychotherapeutic approaches are generic in nature and only minor modifications are required to apply these treatments to patients with depression who are experiencing epilepsy and/or seizures. The programs that are currently under scientific evaluation for treating depression in epilepsy largely follow the general principles of CBT.[155–159]

mediated synaptic inhibition (namely, phenobarbital, primidone, benzodiazepines, valproic acid, gabapentine, tiagabine and vigabatrin) with sedating effects (fatigue, cognitive slowing, weight gain, and anxiolytic and antimanic effects); and drugs that attenuate glutamatergic synaptic excitation (namely, felbamate and lamotrigine) with stimulatory effects (activation, weight loss, and potentially anxiogenic and antidepressant effects). Carbamazepine is classified as 'partially sedating' (no weight gain and no anxiolytic effect), and topiramate falls into both categories, with depression as an important adverse effect.[119]

Depression has long been recognized as an adverse effect of phenobarbital[120,121] and primidone,[122] and this effect is increased by a personal or family history of depression. Several studies have confirmed an antidepressant and mood-stabilizing effect of lamotrigine that is independent of its anticonvulsant effects.[123,124] Levetiracetam showed both negative and positive effects on behavior and mood.[125–127] Titration, mode of drug release and a family history of psychiatric disorders all play a part in determining psychopathological adverse effects of AEDs.[128,129] Clinicians should be aware of the possibility that depression and even suicidal ideation might be caused by AEDs.

Depression correlates from neuroimaging

An increasing number of neuroimaging studies in patients with epilepsy show that depression and suicidality correlate with altered brain structures (measured by MRI and voxel-based morphometry),[130–134] 5-hydroxytryptamine (serotonin) metabolism (measured by PET),[135,136] neurocognitive activation (measured by functional MRI),[137] and hippocampal integrity (measured by magnetic resonance spectroscopy).[138] Generally, the findings from these studies still seem preliminary, inconsistent and hypothesis-generating in nature (for example, unpredicted, high-order interaction effects of several clinical factors have been reported in small samples).

Neurobiological correlates of depression comorbidity, as revealed by neuroimaging, do not necessarily imply a purely neurobiological etiology of depression. These correlates are also compatible with the diathesis–stress model, which predicts that pathophysiological alterations in integrative systems, including the brain, act as substrates for high vulnerability and increased allostatic load.

Epilepsy-related clinical factors

The evidence for some frequently presumed clinical correlations that could corroborate the neuroetiological model of depression in epilepsy was found to be weak on closer examination. The majority of studies on adult patients with epilepsy failed to find evidence for the presumed effects on depression of epilepsy-related factors such as epilepsy duration,[139] type of seizure disorder (epileptic versus nonepileptic, and focal versus generalized),[140,141] seizures (duration and frequency),[139,28] focus site (temporal versus extratemporal, and temporomesial versus temporolateral),[40,140,142] or focus side (left versus right).[36,37,40] In one MRI study, the prevalence of depression in epilepsy was higher in patients without brain lesions than in those with brain lesions.[40] Some recent studies reported an effect of epilepsy type,[143] focus site,[36,144] and focus lateralization[145,146] on psychopathological comorbidities other than depression (for example, anxiety). In another study, more patients with temporal than frontal lobe epilepsy showed depression as a personality trait, but no effect on current depressive disorders was observed.[147]

Treating depression comorbidity

If depression is caused by general psychological mechanisms on the background of epilepsy and stress-related factors, the appropriate therapeutic response will aim to reduce stress—for example, by improving the coping skills (psychotherapy) or the life conditions (rehabilitative care) of the patient. Conversely, if the cause of depression comorbidity is purely neurobiological, the therapeutic approach will be brain-centered—for example, using antidepressant drugs or applying electric and/or magnetic brain stimulation. The efficacy of these different therapeutic approaches provides further evidence regarding the causal mechanisms underlying depression in epilepsy.

Psychotherapeutic approaches

The diathesis–stress model of depression and the paradigm of learned helplessness (also termed an external locus of control) call for interventions focused on cog-

nition and behavior (Box 2). In nonepileptic patients with depression, cognitive behavioral therapy (CBT) was moderately effective with regard to the immediate response and remission rates, irrespective of depression severity.[148,149] In studies comparing CBT and antidepressant drugs, the two approaches were similarly effective, but CBT was advantageous with regard to relapse prevention.[148] CBT was shown to be effective for the treatment of depression comorbidity in patients with chronic somatic conditions.[150] However, a possible publication bias must be considered.[151] Moderate antidepressant efficacy was also shown for acceptance and commitment therapy (ACT)[152,153] and behavioral activation (Box 2);[154] the latter produced better therapy adherence than CBT.

Recently, specific CBT concepts for the treatment of depression in epilepsy were introduced (Using Practice and Learning to Increase Favorable Thoughts [UPLIFT],[155,156] Program to Encourage Active Rewarding Lives for Seniors [PEARLS],[157] Coping Openly and Personally with Epilepsy [COPE],[158] and Epilepsy Awareness, Support and Education [EASE][159]), and promising preliminary outcome data from randomized controlled trials have been reported. Two randomized controlled trials demonstrated positive effects of only a few hours of ACT on HRQOL and even seizures.[160,161] Importantly, CBT has shown potential in preventing depression in newly diagnosed adolescents with epilepsy.[162] Furthermore, CBT yielded moderate to strong effects on mood and seizures in patients with PNES.[163,164] Behavioral activation requires a low level of cognitive self-reflection, and so might be most appropriate for treating depression in patients with epilepsy who have cognitive impairments, as well as for treating types of depression in epilepsy that are associated with somatic rather than cognitive complaints.[165,166]

Psychotherapy can obviously only be effective if it changes brain functions. A pre–post study using functional MRI showed that CBT has the potential to improve the reduced neurocognitive activation of the prefrontal cortex, the temporal lobe (including the hippocampus), and the thalamus in epileptic and non-epileptic patients with depression.[167]

Brain-related approaches

The specific antidepressant efficacy of selective serotonin reuptake inhibitors (SSRIs) in nonepileptic patients with depression was recently questioned by a series of comprehensive meta-analyses, as highlighted in a review.[168] The general impression of a good antidepressant efficacy of SSRIs is biased by selective publication.[169] 94% of the published studies showed positive effects, but only 51% of the studies initially submitted to the FDA showed positive effects. Other studies consistently showed that the efficacy of SSRIs decreased with decreasing baseline severity of depression.[170–172]

On the basis of their clinical experience, almost all experts in the field recommend antidepressants for the treatment of depression in epilepsy, with SSRIs being the first choice,[7,37,173] but general practitioners and neurologists seem reluctant to adopt this approach.[174] Only a few, mostly uncontrolled (single-arm) studies have been conducted. These studies reported no,[175] low,[176] moderate[177,178] or high (pediatric)[179] remission rates in response to antidepressant drugs, as well as adverse effects and low therapy adherence rates.[178,180] Importantly, no seizure exacerbation was observed.[181] In most studies, patients with epilepsy who were receiving antidepressants showed higher depressive mood scores than those who were not receiving these drugs.[2,39,100,101,182]

With regard to the increased risk of suicidality in patients with epilepsy, vigorous antidepressant drug treatment is often strongly recommended for suicide prevention.[7] However, the evidence that antidepressant drugs reduce suicidality is inconclusive. Indirect evidence exists for an antisuicidal effect of antidepressants in the general population,[183,184] but use of SSRIs was also correlated with a small but detectable risk increase for suicidal ideation in adolescents, which resulted in an FDA alert in 2005.[183–185] In the USA, an increasing number of patients have been prescribed antidepressants since the 1980s[1,186] but with no effect on suicide rates (which currently are even increasing, particularly in adult men).[41,187]

Electrical stimulation of the left cervical vagus nerve received FDA approval as an add-on treatment for therapy-refractory epileptic seizures in 1997, and as an add-on treatment for severe therapy-refractory depression

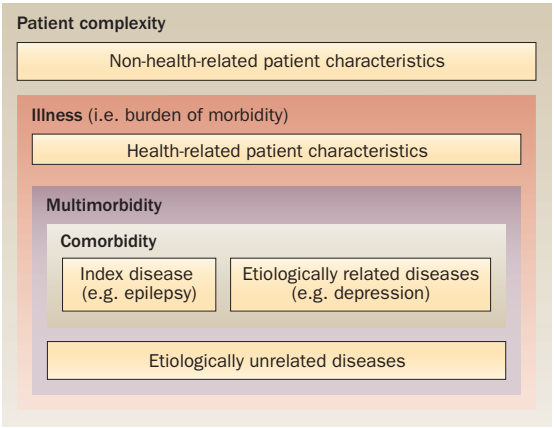

Figure 1 | Patient complexity. Isolated evaluation of disease-related factors in epidemiology is insufficient to determine an individual's burden of morbidity. The novel concept of patient complexity, therefore, considers medical and nonmedical patient characteristics.[192,193] Depending on the research interest, an index disease is defined (for example, epilepsy). Etiologically related, concomitant diseases (for example, depression) are addressed as comorbidities; etiologically unrelated diseases are addressed as multimorbidities. Illness[17] represents the experience of feeling unwell, which depends on disease-related factors and other patient characteristics (for example, age and personality traits). Non-health-related factors such as level of education, socioeconomic and marital status, and quality of social support determine the individual's burden of morbidity. Depression may represent the illness, a health-related personality trait and/or a concomitant psychiatric disorder (comorbidity or multimorbidity, depending on the etiology). Depression comorbidity may be related to the index disease on a purely biological or a psychological basis (diathesis–stress model).

in 2005. However, the two available controlled studies of this approach did not find a positive psychotropic effect in patients with epilepsy.[188,189] Taken together, brain-related treatments may have the potential to reduce depression in epilepsy, but more-compelling evidence for the specific pharmacological or stimulatory therapy effects is required to corroborate the neuroetiological account of depression. In particular, randomized, controlled studies in patients with epilepsy are needed to support the current treatment recommendations.

Conclusions and future prospects

Depression in epilepsy seems to be generally compatible with the diathesis–stress model of depression. Learned helplessness and the burden of epilepsy represent psychological stress-related factors that strongly contribute to the development of depression comorbidity, even in nonepileptic individuals who suffer from the impact of seizures on life. Therefore, the focus of studies on depression in epilepsy should be extended from medical aspects to patient complexity. However, patients with epilepsy also show acute states of depressed mood that arise on a purely neurobiological basis—for example, following seizures. Randomized, controlled interventional studies on the prevention and treatment of depression and suicidality in epilepsy, particularly through the use of drugs, are lacking.

In epilepsy and other neurological diseases, clinicians may tend to reduce depression comorbidity to a brain dysfunction and to underestimate the preventive and therapeutic potential of psychological and rehabilitative approaches. The burden of living with epilepsy and/or seizures deserves more attention and requires multidisciplinary support for the patients.[190] We agree with Brodtkorb and Mula[191] that "health professionals often focus exclusively on medical aspects of the disorder, whereas the stigma, the social disability, and the total burden of the disease are often neglected." In particular, evaluation of the patient's current and past life conditions (including their psychiatric history) should form part of the presurgical work-up.

Our recommendation is in line with recent developments in epidemiology emerging from internal medicine that are shifting the focus from comorbidity or multimorbidity to patient complexity. This novel approach acknowledges that an isolated medical perspective does not allow adequate recognition of the total burden of a disease (Figure 1).[26,192,193]

Two recently published studies on five patients who developed *de novo* depression with suicidal ideation after epilepsy surgery provide evidence for the diathesis–stress model of depression comorbidity and a good model for the recommended integrative neuropsychiatric evaluation.[130,194] Mood outcome was affected neither by the seizure outcome (two patients became seizure-free) nor by co-medication with lamotrigine (all five patients) or other antidepressant drugs (two of five patients). However, all five patients had mesiotemporal lobe epilepsy (two right hemisphere, three left hemisphere) and smaller contralateral hippocampal volumes than other surgical patients with mesiotemporal lobe epilepsy who did not develop depression after surgery. Thus, reduced hippocampal reserve capacity might represent a neural substrate of the diathesis to develop depression after unilateral mesiotemporal lobe resections. Consistent with the diathesis–stress model, marital or other relationship distress occurring after surgery triggered the development of depressive mood in all five patients. Currently, no medical treatment for hippocampal dysfunction is available, but timely counseling and postsurgical rehabilitative care might prevent depression by avoiding additional allostatic load on the impaired brain systems.

Research into the link between epilepsy and depression has been dominated by non-interventional, correlative and single-arm studies, which have a limited capacity to indicate causal relationships. Therefore, more investigator-initiated experimental studies (that is, randomized, controlled trials or matched-control trials if randomization is unfeasible) on innovative approaches to the prevention and treatment of depression comorbidity in epilepsy patients are needed. Interventional studies also promise greater clinical benefits for the affected patients.

The lack of controlled studies on the efficacy and safety of antidepressant drugs is incompatible with the strong focus of the current guidelines on antidepressant drug treatment.[13,173,195] Further studies on the etiology of suicidality and the role of antidepressant drug treatment in suicide prevention are also particularly warranted.[42] Drug treatments, psychotherapy and rehabilitative care should be evaluated in isolation, in combination, and in comparison with each other. In these studies, states of depressive mood should be carefully distinguished from individually diagnosed depressive disorders, and neurobiological, psychological and socioeconomic variables should be regularly considered.

Review criteria

The focus of this Review was on recent patient studies on depression in epilepsy (2008–2010). We searched PubMed using the following search terms (effective date: 20th February 2011): (epilepsy[Title/Abstract] OR seizure[Title/Abstract]) AND depression[Title/Abstract] AND (humans[MeSH Terms] AND English[lang] AND (2008/01/01[PDAT]: 2010/12/31[PDAT]). Non-relevant papers (for example, on 'spreading depression' and/or EEG) were excluded.

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Author contributions

C. Hoppe researched the data for and wrote the article. C. Hoppe and C. E. Elger contributed equally to discussions of the content and to review and/or editing of the manuscript before submission.