Depression in epilepsy: mechanisms and therapeutic approach

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***Abstract*:** In patients with epilepsy, mood disorders represent a frequent psychiatric comorbidity but they often remain unrecognized and untreated. However, comorbid depression may have a major impact on the quality of life of patients with epilepsy, sometimes even more than the seizures. Among the potential neurobiological and psychosocial determinants, epilepsy-related variables (age at onset of seizures, temporal lobe epilepsy and frequency of seizures) and the antiepileptic drug treatment have been associated with depression. Nonetheless, data on treatment strategies are still limited with a lack of controlled trials on the use of antidepressant drugs. Moreover, the issue of psychotropic drug treatment of depression in epilepsy is interlinked with that of worsening seizures. This paper is aimed at discussing all these subjects in the light of current literature on the neurobiology of depression in epilepsy.

***Keywords*:** epilepsy, depression, antiepileptic drugs, antidepressant drugs

Introduction

Medicine has long known that people with epilepsy may suffer symptoms other than seizures. Around 400 BC, the Greek physician Hippocrates observed that 'melancholics ordinarily become epileptics, and epileptics, melancholics: what determines the preference is the direction the malady takes; if it bears upon the body, epilepsy, if upon the intelligence, melancholy' [Temkin, 1971; Lewis, 1934].

Nowadays, it seems well established that reasons for such a close link are both biological and psychosocial [Kanner and Balabanov, 2002]. On one hand, epilepsy is a chronic disorder and as such it brings about social discrimination leading to demoralization, poor self-esteem and a negative perspective towards life. In fact, patients with epilepsy have the ever-ready risk of either becoming unconscious or falling and damaging themselves, and, in public, of social embarrassment. In addition, recent research has pointed out the biological contribution to this association given by neuroanatomical and neurochemical principles such as the involvement of the temporal lobes [Quiske *et al.* 2000] and the psychotropic effects of antiepileptic drugs [Mula and Sander, 2007]. Comorbid depression represents an important issue in the management of people with epilepsy being associated with poor quality of life (QOL) and poor prognosis [Hermann *et al.* 2008].

Gilliam *et al.* [1997] noted depression to be the most important predictor of QOL, representing a more powerful predictor than the actual seizure frequency. These findings have been replicated by a number of authors [Boylan *et al.* 2004; Perrine *et al.* 1995] confirming the importance of the affective state of the patient in QOL and wellbeing. Furthermore, comorbid depression seems to represent a predictor of poor prognosis. People with epilepsy and depression are more likely to experience side effects of anti-epileptic drugs (AEDs) [Kanner, 2007; Cramer *et al.* 2003], are more often drug-refractory [Hitiris *et al.* 2007] and have a poorer outcome after epilepsy surgery [Kanner, 2008] compared with epilepsy patients without depression. For all these reasons, rapid and easy to use clinical instruments screening for depression have been developed specifically for patients with epilepsy (e.g. the NDDI-E) [Gilliam *et al.* 2006]. The aim of this paper is to review available literature on pathogenetic mechanisms of depression in epilepsy and to discuss treatment strategies and implications.

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On the prevalence of depression in epilepsy

A number of limitations affect current epidemiological research of psychiatric comorbidity in epilepsy. On one hand, data coming from selected clinic samples, such as tertiary referral centres, give a bias towards the more severely affected subjects, which are more likely to be on a polytherapy regimen and to be complicated by a number of comorbidities. On the other hand, community-based studies give us good epidemiological estimates but they often lack detailed information on phenomenology of psychopathology and clinical characteristics. In their general-practice study, Edeh and Toone [1987] reported a 22% prevalence of depressive disorders in an unselected sample of patients with epilepsy; these findings have been replicated by another community health survey [Tellez-Zenteno *et al.* 2007]. In both cases, it is evident that prevalence rates of depression are much higher in epilepsy than those reported in the general population – about 12%.

Furthermore, depression seems to be more prevalent in epilepsy when compared with other chronic medical conditions. A large US survey investigated depression in a large unselected sample of patients with epilepsy, comparing the prevalence rates with those of patients with asthma and healthy controls [Ettinger *et al.* 2004]. This study, again, demonstrated that symptoms of depression are significantly more frequent in the epilepsy group (36.5%) rather than in people with asthma (27.8%) and healthy controls. In other neurologic conditions, such as migraine, mood disorders are highly represented as well, with prevalence rates ranging between 14.3% and 18.8% [Mula *et al.* 2008a] and odds ratios ranging between 2.2 and 4.0 [Hamelsky and Lipton, 2006].

Studies from selected patient groups, such as tertiary referral centres or from surgery programs, noted an even higher prevalence of depression than that reported in unselected patient groups up to 58% [Victoroff *et al.* 1994]. A US study conducted in five epilepsy centres noted a 34% prevalence of mood or anxiety disorders defined by DSM-IV criteria [Jones *et al.* 2005] including major depression in a proportion of 19%. A study conducted on patients awaiting temporal lobe epilepsy surgery reported a prevalence rate of major depression up to 21% [Ring *et al.* 1998]. It has been suggested that, in selected patient populations, depression could be related to the recurrence of seizures, speculating on the role of psychosocial variables. This is quite a valid observation. In fact, depression seems to occur in only 4% of seizure-free patients, in about 10% of patients with less than one seizure a month, while rates increase up to 21% in patients with higher seizure frequency and uncontrolled epilepsy [Jacoby *et al.* 1996]. These findings have been replicated by other authors [O'Donoghue *et al.* 1999], suggesting that, indeed, patients with epilepsy and continuing seizures are significantly more likely to suffer from depression than those in remission.

In summary, all this evidence taken together suggests that epilepsy and depression are closely linked and that this association is more frequently reported than in other chronic medical conditions. Moreover, the presence of depression can be said to be even greater in selected populations, reflecting, in a large part, the intractability of the seizure disorder.

The neurobiology of depression in epilepsy

The neurobiological basis of depression in epilepsy has fascinated generations of researchers. Particularly intriguing is the observation that the relationship between epilepsy and depression is not necessarily unidirectional, namely that some patients may present a mood disorder before the emergence of the seizures [Hesdorffer *et al.* 2000; Forsgren and Nystrom, 1990]. A population-based, case-control study reported that patients with epilepsy were 3.7 times more likely to have had a history of depression preceding their initial seizure [Hesdorffer *et al.* 2000] and it is interesting to note that the major depressive episode occurred closer to the date of the first seizure, suggesting that the depressive episode may have facilitated the onset of the seizure disorder.

However, a number of reasons may explain this bidirectional relationship between epilepsy and depression, including the development of epilepsy following suicidal attempts, alcohol or drug abuse or following some other kinds of trauma such as head injury. Nevertheless, the bidirectional relationship does not imply causality but suggests that common pathogenetic mechanisms are operant in both conditions, with the presence of one disorder potentially facilitating the development of the other. Among potentially implicated variables it is important to consider (1) abnormal activity of several neurotransmitters particularly serotonin,

noradrenalin, dopamine, GABA and glutamate; (2) structural changes (identified by high-resolution MRI) in temporal- and frontal-lobe structures, amygdala, hippocampus, entorhinal cortex; (3) functional abnormalities (identified by positron emission tomography and single-photon emission computed tomography) in temporal and frontal lobes, consisting of decreased 5-HT1A binding in the mesial structures, raphe nuclei, thalamus and cingulate gyrus; (4) abnormal function of the hypothalamic–pituitary–adrenal axis [Kanner, 2006] (Table 1).

All of these issues are strictly related to the still unresolved debate about the association with a particular epilepsy syndrome. Some studies have shown patients with temporal lobe epilepsy to be more prone to depression than other groups, but other investigations have failed to confirm this observation. In general terms, it seems to be the case that patients with complex partial seizures [Robertson, 1998] or those with mesial temporal sclerosis [Quiske *et al.* 2000] are more likely to have symptoms of depression. Interestingly, a number of studies in the psychiatric literature suggest an association between hippocampal volume loss and mood disturbances. In 1996, Sheline and collaborators found smaller hippocampal volumes, bilaterally, in ten patients with a history of major depression in remission when compared with hippocampal volumes of ten age-, sex-, and height-matched healthy subjects [Sheline *et al.* 1996].

Table 1. Variables implicated in the pathogenesis of depression in epilepsy.

Patient-related	Premorbid personality Temperament and character features Gender differences
Antiepileptic drug related	GABA augmentation
Epilepsy-related	Psychological Illness representation Coping mechanisms Stigmatization Low expectancy of achievement Biological Hippocampal shrinking Amygdala hypertrophy Head injury Neurotransmitter abnormalities

Moreover, hippocampal volumes inversely correlated with duration of the disease, suggesting that patients with a chronic and active disease were more likely to have hippocampal atrophy. These authors replicated their findings in a larger study [Sheline *et al.* 1999] and, subsequently, a number of publications confirmed their preliminary observations [Frodl *et al.* 2002; Bremner *et al.* 2000], putting beyond doubt the involvement of temporo-limbic structures in mood disorders. In fact, although further research in this area is needed because information about power and effect size is often lacking, neuroimaging studies are revealing an underlying brain network of depression in psychiatric patients without a neurological disorder, which includes the temporal lobes in general and the hippocampus in particular, thus in keeping with the findings in patients with epilepsy.

Older literature tried to establish a 'laterality' effect on depression, meaning that patients with right or left temporal lobe epilepsy were more likely to develop a mood disorder. Many authors have attempted to confirm this laterality hypothesis with very mixed and overall equally balanced results favouring neither the right nor the left hemisphere. Modern laterality hypothesis relate to the connectivity of the mesial temporal lobe and the observation that chronic active temporal lobe epilepsy may be associated with hypoactivity and dysfunction in anatomically connected regions distant from the primary epileptogenic focus. In this regard, left temporal lobe epilepsy may lead to reduced activity in the frontal lobes and such hypoactivity, also known as hypofrontality, has been linked to endogenous depression [Kimbrell *et al.* 2002; Baxter *et al.* 1989]. A number of studies, using brain imaging techniques [Schmitz *et al.* 1997; Bromfield *et al.* 1992] or neuropsychological tests [Hermann *et al.* 1991] supported such a link among frontal lobe dysfunction, depression and temporal lobe epilepsy.

The relationship of antiepileptic drugs to depression

AEDs have a high psychotropic potential beyond their antiseizure effect that needs to be systematically investigated in patients with epilepsy. In fact, this class of compounds is extensively used in psychiatric practice as mood stabilizers [Melvin *et al.* 2008], antianxiety agents [Mula *et al.* 2007] or in withdrawal syndromes [Zullino *et al.* 2004]; however, it is well known that, especially in patients

with epilepsy, AEDs may have negative effects on mood and behaviour.

Current knowledge on psychopharmacology of AEDs suggests that it is possible to distinguish between drugs with potential positive effects on mood, such as carbamazepine and valproic acid, and others with detrimental effects (Table 2). The AEDs most associated with the occurrence of depressive symptoms in patients with epilepsy seem to be those which act at the benzodiazepine–GABA receptor complex, and include barbiturates, topiramate and vigabatrin [Mula and Sander, 2007]. Data on zonisamide are scant while tiagabine, levetiracetam and felbamate seem associated with an intermediate risk and an incidence of depression of about 3% or lower has been reported. The other AEDs show a low incidence of depression (less than 1%).

Within this literature the concept of forced normalization has been revived. This phenomenon describes the development of a psychiatric syndrome when seizures are suddenly switched off [Trimble and Schmitz, 1998]. A psychotic disorder has been very often described, but depressive symptoms have been also reported. This literature is of interest because, while the psychoses appear to be related to complete cessation of seizures, depression is not always associated with complete seizure suppression [Robertson, 1998].

The identification of a clinical phenotype more at risk of developing mood symptoms during AED therapy is important so that clinicians can inform patients and their families and make sure that the patients are monitored closely. In general terms, the use of AEDs in monotherapy, adopting slow titration schedules and low doses when possible, can significantly reduce the incidence of depressive symptoms. Previous histories of a mood disorder or a familial predisposition are important risk factors and should be always kept in mind when choosing the appropriate AED.

Finally, the recent issue of suicide risk with AEDs need to be mentioned. The FDA performed a meta-analysis of 199 placebo-controlled studies of 11 AEDs, used for seizure control, or psychiatric or 'other' indications. There were four completed suicides in those taking AEDs and none in those on placebo. The odds ratio for suicidal behaviour or ideation was 1.8 (95% CI 1.24–2.66) suggesting that people taking AEDs are more at risk than those on placebo. The odds ratio was significantly raised for people taking AEDs for epilepsy, but not for the other indications [US Food and Drug Administration, 2008; Katz, 2006].

The risk of suicidal ideation and behaviour as side effects of AED treatment is very low. Clinicians must, however, inform patients and their family of the FDA's alert, but placing the reported increased risk in a proper perspective. Some people with epilepsy are more likely to develop psychiatric side effects with any AEDs and these people should be followed closely whenever a new AED is introduced. Nonetheless, the risk of suicidality associated with AEDs needs to be balanced, in people with epilepsy, against the risk of not treating the seizures. In fact, the risk

Table 2. Psychotropic effects of antiepileptic drugs.

	Negative	Positive
Barbiturates	Depression, hyperactivity	Anxiolytic, hypnotic
Carbamazepine–Oxcarbazepine	Irritability	Mood stabilizing, antimanic
Ethosuximide	Behavioural abnormalities, psychosis	–
Felbamate	Depression, anxiety, irritability	–
Gabapentin	Behavioural problems in children	–
Lamotrigine	Insomnia, agitation	Mood stabilizing, antidepressant
Levetiracetam	Irritability, emotional lability	Antimanic?
Phenytoin	Encephalopathy	Antimanic?
Pregabalin	?	Anxiolytic
Tiagabine	Depression (Non-convulsive status epilepticus)	Anti-anxiety ?
Topiramate	Depression, psychomotor slowing, psychosis	Mood stabilizing
Valproate	Encephalopathy	Mood stabilizing, antimanic (anxiolytic)
Vigabatrin	Depression, aggression, psychosis	–
Zonisamide	Agitation, depression, psychosis	Antimanic?

of stopping AEDs or refusing to start AEDs for the control of a seizure disorder is significantly worse and may result in serious harm including death of the patient [Bell *et al.* in press].

Treatment strategies for depression in epilepsy

Evidence for treatment strategies of mood disorders in epilepsy still relies heavily on clinical experience and data favouring a particular drug are lacking. During recent years, a number of authors have approached this clinical problem of treating mood disorders in epilepsy from different points of view [Kanner and Balabanov, 2005; Prueter and Norra, 2005; Mula *et al.* 2004] and an expert US panel comprising members from the Epilepsy Foundation's Mood Disorders Initiative have composed a consensus statement [Barry *et al.* 2008]. However, without evidence-based data on the use of antidepressant drugs in patients with seizures, widely accepted guidelines for the treatment of mood disorders outside epilepsy still need to be followed [Trivedi *et al.* 2006].

Data about tricyclic antidepressants are largely uncontrolled but it seems that they can be considered sufficiently safe in epilepsy [Blumer *et al.* 2004]. The only published controlled trial involved amitriptyline and nomifensine, an antidepressant no longer available, showing that nomifensine was superior to amitriptyline after 12 weeks of treatment [Robertson and Trimble, 1985]. Data on new generation antidepressants are limited to a few open studies with sertraline [Thomè-Souza *et al.* 2007; Kanner *et al.* 2000], citalopram [Specchio *et al.* 2004; Kuhn *et al.* 2003; Hovorka *et al.* 2000], reboxetine [Kuhn *et al.* 2003], mirtazapine [Kuhn *et al.* 2003], and fluoxetine [Thomè-Souza *et al.* 2007]. In general terms, all these studies showed good tolerability, but the reported response rates were highly variable, ranging, for example, with citalopram, between 38% [Khun *et al.* 2003] and 65% [Hovorka *et al.* 2000] at 8 weeks. This can be due to a number of reasons such as the selection of patients, the lack of a rigorous psychiatric assessment (it is not often specified whether patients had dysthymia, major depression, bipolar depression, interictal dysphoric disorder etc.), the presence of other comorbid axis I disorders, the presence of brain damage, cognitive impairment, a family history for mood disorders and so on.

Data on psychological therapies for mood disorders in epilepsy are really exceptional. To the best of our knowledge, only two papers, one involving adult patients [Tan and Bruni, 1986] and the other children [Martinovic *et al.* 2006], have been published so far, both of them showing some utility of cognitive behavioural therapies in the management of depression.

The issue of worsening seizures with the prescription of antidepressant drugs represents a major concern for clinicians. The concept that this class of compounds may be likely to produce convulsions began with tricyclics and the most obvious explanation resides in their effect on serotonin and noradrenalin neurotransmission [Jobe and Browning, 2005; Dailey and Naritoku, 1996]. However, available data on seizure risks derive from animal research or studies using *in vitro* techniques. Moreover, data on the prevalence and incidence of seizures in humans come from psychiatric samples [Alper *et al.* 2007], and conclusions from these data are impossible to apply to patients with epilepsy. In general terms, for the majority of antidepressants prescribed at dosages within the therapeutic range, the incidence of seizures is less than 0.5% when other risk factors are excluded. The only compounds that may pose a risk of seizures include mianserine, clomipramine and maprotiline (Table 3). The risk associated with bupropion appears to be acceptably low and in line with that of other antidepressants when prescribed as slow release formulation [Mula *et al.* 2008b].

Table 3. Prevalence of seizures during therapy with antidepressant drugs (data from psychiatric populations without epilepsy) [Mula *et al.* 2008b; Alper *et al.* 2007].

Antidepressant	Drug dose	Seizure prevalence (%)
Amitriptyline	<200 mg	0.1
	>200 mg	0.6
Imipramine	50–600 mg	<0.1–0.9
Clomipramine	>200 mg	0.5
Maprotiline	150–200 mg	0.4
Fluoxetine	20–60 mg	0.2
Fluvoxamine	<100 mg	0.2
Sertraline	50–100 mg	<0.1
Paroxetine	20–60 mg	0.1
Bupropion	300 mg SR	0.1
	300–450 mg IR	0.4
	>450 mg IR	>0.6
Mirtazapine	30 mg	<0.1

Conclusions

Depression in epilepsy represents a frequently encountered psychiatric comorbidity. This is probably related to a number of variables that are both biological and psychosocial. In patients with a previous history of depression, some AEDs, particularly GABAergic agents such as vigabatrin, tiagabine, topiramate and barbiturates, should be carefully used as they can be associated with a worsening of the psychiatric symptoms. Clinicians need to be aware that, although rarely, a sudden reduction of seizures may precipitate the onset of depressive symptoms, a phenomenon also known as forced normalization.

Antidepressant drug treatment, especially with SSRIs such as sertraline, citalopram and paroxetine, can be safely used in subjects with epilepsy. Neurologists or epileptologists should refer to local psychiatric services all patients with suicidal ideation, psychotic symptoms or unsuccessful trials with at least two different antidepressant drugs. Controlled studies in patients with epilepsy are needed to develop standardized guidelines for the treatment of comorbid mood disorders.

Conflict of interest statement

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