Depression in Epilepsy – Mechanisms and Therapeutic Approaches

a report by

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It has been known for a long time that there are associations between epilepsy and depression, and there are several reasons why the two disorders may be closely linked. Epilepsy is a chronic disorder that brings about social restrictions and discrimination. As with any chronic disorder, epilepsy may be expected to be linked to demoralisation and a negative perspective on life. Furthermore, patients with epilepsy run the unpredictable risk of becoming unconscious. This can mean that they fall and hurt themselves and/or suffer social embarrassment. Recent research, while reinforcing this association, has also pointed out a biological contribution to the association based on neuroanatomical and neurochemical principles.[1] Associations between antiepileptic drug prescription and depression have been another focus of attention.[2]

Epilepsy and Depression – A Bi-directional Relationship

Assessing the prevalence of depression from selected clinical samples of patients with epilepsy shows a bias towards the more severely affected subjects. A better understanding of co-morbid psychopathology comes from community studies. Edeh and Toone[3] carried out a general practice study in the UK and reported that 22% of unselected patients with epilepsy were diagnosed as having a depressive disorder. A Canadian Community Health Survey (CCHS) examined 253 people with epilepsy using a rating scale to identify a history of depression. The authors noted a 22% lifetime prevalence of depression that was much higher than the 12% prevalence rate reported in the general population.[4]

More recently, Ettinger et al.[5] assessed depression in 775 subjects with epilepsy and compared the prevalence rates with those of patients with asthma and with healthy controls. In this study a rating scale assessment was also used (the Center For Epidemiological Studies – Depression Scale [CESD]). Symptoms of depression were significantly more frequent in the epilepsy group (36.5%) compared with those with asthma (27.8%) and controls (11.8%).

Several studies have noted a correlation between depression and seizure frequency. In an epidemiological study, Jacoby et al.[6] noted that depression occurred in 4% of seizure-free patients and in 10% of patients suffering less than one seizure a month, but at a rate of 21% in patients with higher seizure frequency. O'Donoghue et al.[7] noted that patients with epilepsy and continuing seizures were significantly more likely to suffer from depression than those in remission (33 versus 6%).

There are a number of studies from selected patient groups that noted an even higher frequency of depression in these populations. Victoroff et al.[8] evaluated 60 patients with intractable complex partial seizures using a structured clinical interview from the *Diagnostic and Statistical Manual of Mental Disorders 3rd Edition* (DSM-IIIR), and observed that 58% had a lifetime diagnosis of depressive disorders. Jones et al.[9] examined 199 patients from five epilepsy centres, again using a structured clinical interview, the Mini International Neurophychiatric Interview (MINI), and noted that 34% met diagnostic criteria for a mood or anxiety disorder and 19% met criteria for major depression. Ring et al.[10] examined 60 patients awaiting temporal lobe epilepsy surgery, and reported at pre-operative assessment that a major depressive disorder was present in 21%. Taken together, these data suggest that epilepsy and depression are frequently linked, and that the association is more common than in some other chronic medical conditions. Moreover, this relationship seems to be stronger in those with higher seizure frequencies and with continuing seizures. Thus, the presence of depression can be said to be even higher in selected populations, in particular in patients with difficult-to-treat or drug-resistant seizures.

A verified finding is the association between depressive symptoms and quality of life (QOL) in people with epilepsy. Gilliam et al.[11] noted depression to be the most important predictor of QOL, being a more powerful predictor than the actual seizure frequency. Perrine et al.[12] and Boylan et al.[13] have reported similar findings.

An interesting finding is that the relationship between epilepsy and depression is not necessarily unidirectional. Patients with co-morbidity do not always present with the seizure disorder before the emergence of the depression. In fact, it has been noted in epidemiological studies that having a prior mood disorder can be associated with an increased risk of epilepsy.[14,15] There may be a number of reasons for this, including the use of proconvulsive antidepressants and the development of epilepsy following suicidal attempts, drug abuse or some other trauma (e.g. head trauma). However, these findings may reflect on an underlying common pathogenesis, which may relate to an as yet unknown genetic factor or a link with neuro-transmitter function. Certain transmitters, such as serotonine, glutamate and γ-amino butyric acid (GABA), are known to play a role in both epilepsy and depression.

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The Relationship of Epilepsy Syndromes to Depression

There has been considerable debate as to the association between any particular epilepsy syndrome and depression. People with lesional temporal lobe epilepsy are more likely to have intractable seizures and to be taking more extensive medication than those with non-temporal lobe epilepsy. Therefore, they may be at an increased risk of developing depression. Thus, 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.

Examining the relationship between depression and type of temporal lobe epilepsy, Quiske et al.[16] found that patients with temporal lobe epilepsy and mesial temporal sclerosis were more likely to report symptoms of depression than patients with neocortical temporal lobe pathology. In general terms, it seems that patients with complex partial seizures are more likely to have a depressive disorder.[17] With regards to the temporal lobe association with depression, it is of interest that there are a number of studies outside the field of epilepsy in the psychiatric literature that suggest an association between hippocampal volume loss and affective disturbances.[18,19] Thus, although further research in this area is needed, neuroimaging studies are revealing an underlying brain network of depression in psychiatric patients without a neurological disorder, in keeping with the findings in patients with epilepsy.

There are studies linking frontal lobe dysfunction to depression in epilepsy. The latter have emerged from investigations using brain imaging (positron emission tomography [PET] or single-photon emission computed tomography [SPECT]) and neuropsychological batteries. Hermann et al.[20] noted that patients with temporal lobe epilepsy and depression were more likely to perform poorly on frontal lobe neuropsychological tasks, especially with a left-sided seizure focus. Schmitz et al.[21] noted similar frontal changes and localisations using SPECT, and, using PET, Bromfield et al.[22] reported that patients with temporal lobe epilepsy and associated depression revealed bilateral reductions of frontal lobe metabolism, a phenomenon also called 'hypo-frontality'. Although these studies were on a limited number of patients, concordance between the findings supports an anatomical association between temporal lobe epilepsy, depression and frontal lobe dysfunction.

The Relationship of Antiepileptic Drugs and Depression

The association between barbiturates and depression is well-known, but more recent data suggest that it is possible to distinguish between antiepileptic drugs (AEDs) with the potential to have positive effects on mood, such as carbamazepine and valproic acid, and others likely to have detrimental effects (see *Table 1*).

The role of AEDs in precipitating depression is of considerable interest following the introduction of a spectrum of compounds referred to as 'new AEDs'.[2] Within the literature, the concept of forced normalisation has been revived. This phenomenon describes the sudden switching off of seizures in people with long-lasting epilepsy, followed by the development of an alternative psychiatric syndrome. Very often this is a psychotic disorder, but affective symptoms have been also reported.[23–25]

The AEDs most often associated with the occurrence of depressive symptoms seem to be those that act at the benzodiazepine-GABA receptor complex, and include barbiturates, tiagabine, topiramate and vigabatrin. As in psychiatric practice it is known that benzodiazepines and other GABA agonists are clinically associated with depression, and that abnormalities of cerebrospinal fluid GABA have been reported in patients with depression,[26] the link between sudden cessation of seizures, GABAergic agents and the onset of depression seems reasonably secure. Furthermore, these studies have revealed that patients with epilepsy and a prior history of an affective disorder are more likely to develop depression in these circumstances.

Table 1: Psychotropic Properties of Antiepileptic Drugs

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

Treatment Strategies for Depression in Epilepsy

It is important to state that there has been only one controlled trial of the effects of an intervention for mood disorders in epilepsy, and the evidence for treatment strategies relies heavily on clinical experience. Psychiatric symptoms that are temporally related to the occurrence of seizures do not need any specific psychotropic treatment, and a better control of seizures is often the most effective solution.

In the case of a mood disorder characterised by symptoms occurring independently of seizures, psychopharmacotherapy may be required, but evidence in favour of a particular drug is lacking. The only published controlled trial involved nomifensine, an antidepressant that is no longer available.[27] Selective serotonin re-uptake inhibitors (SSRIs) have become the first-line drug treatment for primary major depression and dysthymic disorder in psychiatric practice. However, studies about efficacy and safety in epilepsy are lacking. During recent years, a number of authors have approached the clinical problem of treating mood disorders in epilepsy from different points of view.[28–30] A few open studies have been published about the efficacy of sertraline,[31,32] citalopram,[33–35] reboxetine,[34] mirtazapine[34] and fluoxetine.[32] The study by Thomè-Souza et al.[32] is of particular interest because it is the only published paper involving children and adolescents with epilepsy and depression.

Table 2: Seizure Risk Associated with Some Antidepressant Drugs in the General Psychiatric Population

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

IR = immediate release; SR = sustained release.

In general terms, all presented studies showed antidepressant drug treatment to be well tolerated, but the reported response rates varied greatly; for example, with citalopram response rates ranged from 38[34] to 65%[35] at eight weeks. It is evident that the reported variability is influenced by the selection of patients. The lack of a rigorous psychiatric assessment for a correct diagnosis, the presence of other co-morbid axis I disorders, the presence of brain damage, cognitive impairment and a family history of mood disorders can all affect results. Very rarely are all these variables taken into consideration in studies, but they are essential for a correct interpretation of data.

If studies about psychoactive drugs in epilepsy are rare, studies about psychological therapies for mood disorders in epilepsy are extremely exceptional. We are aware of only two papers on the subject, one involving adults[36] and the other children.[37] Both showed some utility of cognitive behavioral therapies in the management of mood disorder symptoms in epilepsy.

The issue of psychotropic drug treatment of depression in epilepsy is inter-linked with that of the proconvulsant or anticonvulsant effects of antidepressants (see *Table 2*). Tricyclic antidepressants developed a clinical reputation for convulsant liability soon after their introduction.[38] The concept that antidepressant medications are more likely to produce convulsions in patients with epilepsy than in patients without this disorder is intuitively appealing, and seemingly compatible with the concept that seizure predisposition is fundamental to the definition of epilepsy. However, it is clear that the biology of seizure predisposition is not a single entity. Moreover, it is not clear whether the risk of seizure expression arises from the seizure liability itself or from a more complex predisposition inherent in the mechanisms of co-morbidity between affective disorders and epilepsy.[39] A recent meta-analysis comparing seizure risks in controlled trials with antidepressants in psychiatric patients demonstrated lower seizure rates in patients using new antidepressants versus patients in the placebo arms, suggesting that some of the newer antidepressants may have anticonvulsant properties. This has also been shown in experimental studies.[40]

Conclusions

Depression in epilepsy represents a frequently encountered psychiatric complication. It is likely to be related to a number of variables that are both biological and psychosocial. At one time, arguments for the majority of the clinical presentations being explained by psychosocial factors were prominent. However, the literature suggests that the link between depression and epilepsy may not be unidirectional, further supporting the hypothesis of common underlying biological reasons.

Depression in epilepsy can be phenomenologically different from the usual forms of depression and it is essential that treating physicians assess for these varied forms as well. Antiepileptic drugs, particularly GABAergic agents such as vigabatrin, tiagabine, topiramate and phenobarbitone, can be associated with psychiatric treatment-emergent adverse effects such as depression. The newer antidepressants, especially SSRIs such as sertraline, citalopram and paroxetine, do not lower seizure threshold and can be safely used to treat depression in individuals with epilepsy and depression. A sudden reduction in seizures may precipitate the onset of affective symptoms. Clinicians should be aware that the mental state of their patients needs to be carefully reviewed as part of the general epileptological evaluation for a better management and therapy tailored to the needs of each patient. ■

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