Review article

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Depression in epilepsy: phenomenology, diagnosis and management

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ABSTRACT – 1) Depression is a common and important accompaniment of epilepsy. 2) Depression in epilepsy is phenomenologically different from the usual forms of depression and it is essential that treating physicians assess for these varied forms as well. 3) Depression in epilepsy may be managed more effectively if the relationship to the ictus is better understood. 4) Other factors such as stressful life events, related or unrelated to epilepsy, may contribute to the depressive symptoms. 5) Antiepileptic drugs, particularly GABAergic agents such as vigabatrin, tiagabine, topiramate and phenobarbitone are depressogenic in nature. 6) The newer antidepressants, SSRIs such as sertraline, citalopram and paroxetine do not lower seizure threshold and can be safely used to treat depression in epileptic individuals. Fluoxetine may be avoided because of its longer half-life.

Key words: epilepsy, depression, classification, etiology, treatment, SSRI

"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 intelligence, melancholy" (Lewis, 1934).

Epilepsy is the most common serious, neurological condition, the usual prevalence figure quoted being 5-10 per 1000 persons excluding febrile convulsions, single seizures and inactive cases (Macdonald *et al.* 2000, Goodridge and Shorvon 1983, Hauser 1975). The risk of having a non-febrile seizure at some point in an average person's lifetime (lifetime prevalence) ranges between 2 and 5%.

Depression is one of the most frequently reported, co-morbid psychiatric conditions in patients with epilepsy. Prevalence figures ranging from 20-55% in patients with recurrent seizures, and 3-9% in patients with controlled epilepsy have been reported (Jacoby *et al.* 1996). A population-based survey investigating the lifetime prevalence of depression in epilepsy, diabetes and asthma reported 29% of patients with epilepsy having at least one episode of depression, as compared with 16 and 17% prevalence in patients with diabetes and asthma respectively and 8.7% in healthy respondents (Blum 2002).

Historical background

The first organized description of psychiatric disorders in epilepsy was attempted by Falret (Falret 1860/1861) and Morel (Morel 1860). They emphasized the periodicity of mental changes in epilepsy and the prominence of outbursts of anger and fury in their patients. Kraepelin (Kraepelin 1923), in his textbook stated that peri-

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odic dysphorias represent the most common psychiatric disorders in epilepsy. These dysphoric episodes are characterized by irritability with or without outbursts of fury. Depressive moods, anxiety, headaches and insomnia were described as frequent accompaniments. Kraepelin also described the dysphoric episodes as beginning and terminating suddenly, recurring at fairly regular intervals in a uniform manner and lasting for a few hours to two days. Interictal hallucinatory and delusional episodes were viewed as a mere expansion of dysphoric moods by Kraepelin. Bleuler (Bleuler 1949) gave a similar description of the dysphoric disorder of epilepsy.
One of the earliest modern investigations to assess psychiatric co-morbidity in patients with epilepsy was carried out by Pond and Bidwell (Pond and Bidwell 1959/60). They found that 29% of patients had psychological disorders of sufficient severity to seek treatment. Subsequently, Jalava and Sillanpaa (Jalava and Sillanpaa 1996) in a prospective, population-based cohort study demonstrated that subjects with epilepsy are at a higher risk of developing co-morbid psychiatric illness when compared with population-based controls. Overall, the available evidence supports the concept of an overrepresentation of common mental disorders in epilepsy (Krishnamoorthy 2001, 2002, 2004).

Phenomenology of depression in epilepsy

Controversy exists regarding the phenomenology of depression in epilepsy. While Betts (Betts 1974) reported a more endogenous presentation, Mulder and Dally (Mulder and Dally 1952) comment on a more reactive nature of depression associated with epilepsy. Mendez (Mendez *et al.* 1986), on comparing 20, hospitalised, depressed patients with epilepsy with 20 patients suffering from depression alone commented that patients with epilepsy and depression have significantly fewer neurotic traits such as anxiety, guilt, rumination, hopelessness, low self-esteem and somatization. These patients however, had significantly more psychotic symptoms such as paranoia, delusions and persecutory auditory hallucinations. Between episodes of major depression, patients with epilepsy tended to be dysthymic, with irritability and humorlessness. Although it is widely accepted that the phenomenology of depression in epilepsy differs from depression associated with other neurological disorders, confirmatory studies ascertaining are limited in number as well as impact. The phenomenology is also often blurred by the possible side-effects of anti-epileptic agents.

Dietrich Blumer's description of dysphoric disorders in epilepsy is among the most fascinating (Blumer 2000). According to Blumer, psychiatric symptoms exist along a continuum, from dysphoric disorder with fleeting symptoms, to a more severe dysphoric disorder with prominent but transient psychotic features, to a disorder with more prolonged psychotic states. Blumer also put forward the concept of subictal dysphoric disorders (Morel 1860, had earlier described "masked epilepsy"), a psychiatric symptom complex identical to that observed in patients with epilepsy, but in the absence of seizures. The similarities between premenstrual dysphoric disorder and dysphoric symptoms in epileptic women led him to conclude that premenstrual dysphoric disorder was a variant of subictal dysphoric disorder and needed to be treated with a combination of antidepressants and antiepileptics.

Impact of depression

Co-morbid depression can have significant physical, social and financial consequences, including increased drug use, poor quality of life, social disability, and mortality (Barry *et al.* 2000). Begley (Begley *et al.* 2000) studied the lifetime and annual cost of epilepsy in the United States and found that the indirect costs in terms of disabilities and socioeconomic conditions on foregone earnings and household activity account for 85% of the total costs. They further concluded that, "epilepsy is unique in the large proportion of costs that are productivity related". Cramer, in an assessment of the impact of co-morbid depression on health care utilization and health care coverage by people with epilepsy in US, found that people with untreated depression used significantly more health resources of all types. Patients with untreated depression also varied significantly in terms of health care utilization according to the severity of their depression (Cramer *et al.* 2004).

Depression or psychological distress have been shown to be the strongest predictors of health-related quality of life, even including seizure frequency and severity, employment, or driving status (Gilliam *et al.* 2003). Interictal anxiety and depression can exert independent adverse effects on health-related quality of life (HRQOL). In addition, frequent, severe, and chronic seizures also reduce HRQOL, but appear less powerful predictors of HRQOL than interictal psychiatric symptoms. Recognition and treatment of co-morbid depression and anxiety thus form an important consideration in improving quality of life in epilepsy (Johnson *et al.* 2004).

The suicide rate in epilepsy is five times greater than that in the general population (Harris and Barraclough 1997). Suicides in epilepsy do not necessarily occur when treatment is unsuccessful; but often occur unexpectedly when patients are forced to change their lives when they become seizure-free (Janz 1988). The most common Axis I diagnosis among individuals with current suicidal ideation has been established to be current major depressive episode (Jones *et al.* 2003).

Classification issues

Although the tradition in modern psychiatry is to adhere to the classification systems such as ICD-10 (WHO, 1992) and DSM-IV (APA, 1994), it is well accepted today that psychopathology in disorders such as epilepsy transcends these conventional descriptions and has unique manifestations that are poorly reflected in these established classifications (Krishnamoorthy 2000). Depressive symptoms and disorders in epilepsy are therefore best classified according to their temporal relationship to the ictus.

1) *Pre-ictal depression*: prodromal depressive moods or irritability can occur hours to days before a seizure, and are often relieved by the convulsion (Lambert and Robertson 1999, Devinsky and Bear 1991). The 19th century psychiatrist Grule (Grule 1930) quotes "*physician and attendants do hope for a seizure in these often very difficult patients, which comes like a salvation for everybody: the patient is much more bearable for weeks thereafter*".

In a prospective study examining prodromal mood changes, Blanchett and Frommer (Blanchett and Frommer 1986) found that most patients reported more depression on the days immediately preceding their seizure than on interictal days, along with an improvement of mood after the seizure. The low mood has been hypothesized to be a symptom of subclinical seizure activity or biological processes involved in the initiation of both depression and seizures.

2) *Ictal depression*: depression can occur as a part of the ictus itself. Ictal depression classically is of sudden onset and occurs out of context, i.e. is not related to environmental stimuli. It can occur in isolation or within seconds to minutes of a CPS and/or secondarily generalized seizure. Ictal depression appears to be more common in patients with TLE (Williams 1956), in whom rates of over 10% (Weil 1959, Devinsky *et al.* 1991) have been reported. Williams (Williams 1956) described depression as part of an aura in approximately 1% of his series of 2000 patients. The severity of ictal depression can range from mild feelings of sadness to profound helplessness and despair. Suicide has been reported during ictal depressive episodes (Lim *et al.* 1986, Betts 1993).

3) *Postictal depression*: although depression lasting hours to days after seizure has been described in some patients, it is rare to find a patient with postictal depression alone (Blumer 1992). Most patients also experience episodes of interictal depression. Postictal depression occurs more commonly after CPSs originating in the right temporal structures, and more prominently with bilateral limbic dysfunction. It has been postulated that postictal depression is a consequence of the inhibitory mechanisms involved in the termination of the seizures.

Depressive disorders which occur peri-ictally are usually short lasting and self-limiting.

4) *Interictal dysphoric disorder*: more recently, in 1998, (Blumer, 1998) drew attention to a peculiar mood disorder seen in patients with refractory epilepsy, particularly TLE. Interictal dysphoric disorder is characterized by a constellation of eight symptoms and requires the presence of any three.

Labile depressive symptoms	Labile affective symptoms	Specific symptoms
Depressive mood	Fear	Paroxysmal irritability
Anergia	Anxiety	Euphoric moods
Pain		
Insomnia		

Interictal dysphoric disorder is typically of short duration and occurs in various permutation and combinations. These symptoms occur at various intervals and tend to last from hours to two or three days. In women, these symptoms become accentuated in the premenstrual period. Blumer stressed that patients with several of the above symptoms maybe at increased risk of sudden, unexpected suicide attempts and also development of interictal psychosis.

Etiology of depression in epilepsy

Forced normalization

In the 16th century, Cardenus (Whitwell 1936) wrote about a case of melancholia alternating with epilepsy, describing what is possibly the first case of forced normalization associated with epilepsy. The term forced normalization was coined by Heinrich Landolt (Landolt 1953) and defines a phenomenon characterized by the fact that with the occurrence of psychotic states, the EEG becomes normal or more normal compared to previous recordings. Although forced normalization clinically usually manifests as a schizophrenia-like psychosis, prepsychotic dysphoria and depression have also been reported (Wolf 1984). Several studies have also reported a decrease in seizure frequency prior to the onset of depressive illness (Dongier 1959/60, Flor-Henry 1969). A decrease in the seizure frequency and thus forced normalization can be brought about by (Robertson 1998):
1) a spontaneous reduction in seizures,
2) antiepileptic drugs,
3) temporal lobectomy.
The phenomenon of forced normalization forms an interesting interface between neurology and psychiatry, with various theories being suggested to explain the same. While Wolf *et al.* (1991) suggested the condition to be a form of active but restricted subcortical seizure activity, various others have postulated that amygdaloid and limbic kindling might play a role in the development of this phenomenon (Krishnamoorthy, 1998). The roles of the

glutamate and the GABA receptors in the mechanisms of epilepsy and psychosis also suggest the possibility of the involvement of various neurotransmitters in forced normalization (Krishnamoorthy 1999). One of the most recent hypotheses put forward to explain the same, digresses towards a more physiological view involving dysfunctions of the ion channels, and suggests that the phenomenon of forced normalization could be a unique kind of channelopathy (Krishnamoorthy 2002).

AEDs and depression

Anti-epileptic drugs may cause significant psychiatric side effects. Kanner (Kanner *et al.* 2000) studied 100 patients who were treated for depression in epilepsy. In almost a third of these patients, the depression was considered iatrogenic, provoked by AEDs. The AEDs, which have been commonly reported as depressogenic, are vigabatrin (10%), tiagabine (5%), topiramate (15%) and phenobarbitone (Trimble 1998). Levetiracetam therapy was associated with depression in 2.5% individuals; this was dose-dependent and was also related to a past history of febrile seizures and status epilepticus (Mula *et al.* 2003).

Laterality hypothesis

In the late 1960s, Flor-Henry (Flor-Henry 1969) postulated that affective disorders were more common in patients with right-sided temporal lobe epilepsy. Many investigators have subsequently reported mixed and overall equally balanced results, favouring neither the right nor the left hemisphere. Modern laterality hypotheses relate to the connectivity of the mesial temporal lobes; left temporal epilepsy may lead to frontal lobe dysfunction (hypofrontality) and clinical depression (Schmitz 2002). Evidence from FDG-PET (Bromfield 1992) and HMPAO-SPECT (Schmitz *et al.* 1997) studies also suggest a difference in the psychopathology of depression in left-sided TLE as compared to right-sided TLE. Victoroff (Victoroff *et al.* 1994), suggested that in individuals with left-sided epileptogenicity, there is a progressive vulnerability to depressive "decompensation". This "laterality hypothesis" has, however been challenged by Quiske (Quiske *et al.* 2004), who noted a similar preponderance of depressive symptoms in both right and left-sided pathologies. Depression in left-sided epilepsy has been hypothesized to be a consequence of seizure activity. This has been confirmed (as above) by Reuber (Reuber *et al.* 2004), who found that following left-sided lobectomy, only patients who became seizure-free improved with respect to mood. Patients with left-sided epilepsies who did not become seizure-free and patients with right-sided TLE however, did not improve.

Endocrine and metabolic factors

The ictus is known to be associated with a wide range of changes in the levels of norepinephrin, tryptophan and 5HIAA, all of which have been implicated in theories regarding the development of depression (Meldrum 1991).

Psychological factors

Epilepsy is associated with repeated and unpredictable episodes of loss of consciousness. This unpredictability and uncontrollability has been compared with Seligman's concept of "learned helplessness", which occurs when patients are exposed to adverse experiences on a random basis (Abramson *et al.* 1978, Hermann 1979, DeVellis 1980). Another concept used to explain depression in patients with epilepsy and depression is the "burden of normality" that describes psychiatric decompensation in a person who is cured from a chronic illness (Schmitz 2002). This may happen when a person loses illness-associated privileges and is forced to meet the everyday challenges of a healthy person. The occurrence, as well as the anticipation of occurrence of seizure, can also act as a serious impediment in the well-being of the individual, thus adding to the psychological burden of the individual.

Risk factors for depression

Depression in epilepsy is multifactorial in nature and has been shown to be influenced by a number of factors.

Gender

In contrast to the increased prevalence of depression in females, a number of the studies have found men to be at a greater risk of depression as compared to females (Fenton 1986, Septien *et al.* 1993, Strauss *et al.* 1992).

Sinistrality

Some studies (Ashtuler *et al.* 1990) have observed that left-handed people with epilepsy have an increased prevalence of psychiatric morbidity, especially depression. A possible explanation advanced is that the expression of left-handedness may indicate early brain injury.

Related neurological conditions

The causative neurological condition responsible for the epilepsy such as multiple sclerosis, cerebrovascular accidents, dementia and head injury may be associated with depression. Taylor (Taylor 1972) and Koch-Weser (Koch-Weser *et al.* 1988) suggested depression to be more common in patients with a structural lesion; this however, has been refuted by other investigators (Hermann 1989).

Genetic

Family history of psychiatric illness, usually depression (Robertson *et al.* 1987) and suicide (Hancock 1971), has been associated with an increased incidence of depression.

Structural changes in the medial temporal lobe

There is an emerging literature that links amygdala enlargement (Tebartz van Elst 1999) and hippocampal atrophy (Baxendale 2005) with depression (and other forms of psychopathology) in epilepsy. While the findings are by no means ubiquitous, they pose interesting questions about the role of these structures in the development of depression and the differentiation between its characterological and symptomatic components.

Past history

Past history of behavioural disturbance in infancy (Moller 1990), neurotic disorders (Roy 1979), deliberate self-harm (Palia, 1986) and depression (Lund 1985) have all been implicated in the development of depression.

Learning disabilities and IQ

Patients with learning disability and concomitant epilepsy have been shown to have twice the percentage of psychiatric disorders (including behaviour problems and autism) as compared with patients with epilepsy (Mignone *et al.* 1970). Psychiatric disorders are also more common in patients who had experienced seizures in the preceding year and have been found to be inversely proportional to IQ.

Age-at-onset and duration of epilepsy

Although most studies have found no relationship between age-at-onset or duration of epilepsy and depression, some studies have described an increased prevalence of depression in patients with late-onset epilepsy (Hermann *et al.* 1996).

Seizure type

A number of studies have reported depression to be more common in patients with CPS (Lambert 1999), and in individuals with MTS (Quiske *et al.* 2000). Controversy however, exists over the prevalence of increased psychiatric morbidity in patients with TLE, with studies for and against the same.

Stigma

Epilepsy has long been associated with satanic possession and evil. A positive relationship has been shown between perceived stigma and affective disorders (Hermann *et al.* 1996).

Psychosocial factors

Patients with a pessimistic, attributional style have an increased prevalence of depression (Hermann *et al.* 1996). Other factors such as increased, stressful life events, poor adjustment to seizures and financial stress have also been associated with increased depression.

Management of depression in epilepsy

Treatment of psychiatric disorders in epilepsy is largely opinion-led, with little evidence from systematic randomized control trials (Krishnamoorthy 2003).
Pre-ictal and ictal depression do not usually require treatment; an improvement in seizure frequency reduces the occurrence of these forms of depression (Lambert 1999) Medications such as benzodiazepines e.g. clobazam, and behavioural methods such as progressive muscular relaxation, biofeedback, and yoga may abort or prevent the development of the attack. The general guidelines for management of depression in epilepsy include the following points.

Antidepressants

Management of depression in epilepsy with antidepressants involves three major issues:
a) effect of antidepressants on seizure threshold,
b) antidepressant-anticonvulsant interactions,
c) efficacy of antidepressants in this category of patient.

Chronic inhibition resulting in psychiatric disorders requires pharmacological intervention directed against this. The presence of dysphoric disorders in patients with epilepsy indicates the presence of marked inhibition. The proconvulsant nature of antidepressants appears to serve as effective antagonists to excessive inhibition. Patients with primary generalized seizures tend to have lower seizure thresholds, and antidepressants must be used with caution in these patients. Within certain concentration ranges, raised levels of extracellular serotonin have been shown to have converse anticonvulsant properties in animal studies (Clinckers *et al.* 2004).
Virtually all non-MAOI antidepressants, including the newer antidepressants such as citalopram, paroxetine, reboxetine and sertraline lower the seizure threshold in varying degrees (Trimble 1978b, Edwards 1985). Robenstein (Robenstein *et al.* 1993) suggested that SSRIs are less seizurogenic as compared to TCAs. Antidepressants and anti-epileptic drugs can affect each other's levels, with anti-epileptic drugs usually reducing antidepressant levels and antidepressants increasing anti-epileptic drug levels (Robertson 1998a, Robertson 1998b). Davis and Glassman (1989) in a recent review found that 65% patients on imipramine improved as compared with only 30% on placebo. Trimble and Robertson (1985), in a placebo-controlled double-blind study however, showed that there were no significant differences between either active drug and placebo in the first six weeks of treatment.

Psychological therapies

Several models of cognitive behavior therapy, ranging from more generic applications to more specific models based on original research, have been applied in epilepsy. In a recent meta-analysis of psychological therapies in

epilepsy however, Ramaratnam (Ramaratnam *et al.* 2001) concluded that, "in view of the methodological deficiencies and limited number of patients studied, we have found no reliable evidence to support the use of treatments and further trials are needed".
The brief form of psychotherapy, group psychotherapy, patient support groups, relaxation therapy, and EEG biofeedback have all been shown to be effective.

Electroconvulsive therapy

Despite a few sporadic reports of spontaneous seizures after ECT (Devinsky 1983, Grogan *et al.* 1995), major studies have found the incidence of spontaneous seizures following ECTs to be lower than the incidence of epilepsy in the general population (Blumenthal 1955, Blackwood *et al.* 1980). ECT may be life-saving in some patients with depression, particularly severe or psychotic depression not responding to antidepressants. The efficacy of the ECT may, however, be reduced by anti-epileptic drugs. Weiner and Coffey (1993) recommend that, with the exception of patients at high risk for status epilepticus or with recent generalized tonic-clonic seizures, AEDs should be omitted the morning before each ECT treatment.

Novel treatments such as vagal nerve stimulation have recently been shown to have a positive effect on both epilepsy and co-morbid depression (Harden *et al.* 2000, Elger *et al.* 2000).

Finally, transcultural issues need to be addressed, and treatment approaches have to be tailored to meet the individual needs of the patient. Krishnamoorthy (2003), in a recent review, pointed out that while western patients and wealthier Asian patients welcome psychological explanations, patients from the lower socioeconomic groups in these settings may find these less acceptable. It is important that patients must be treated until complete

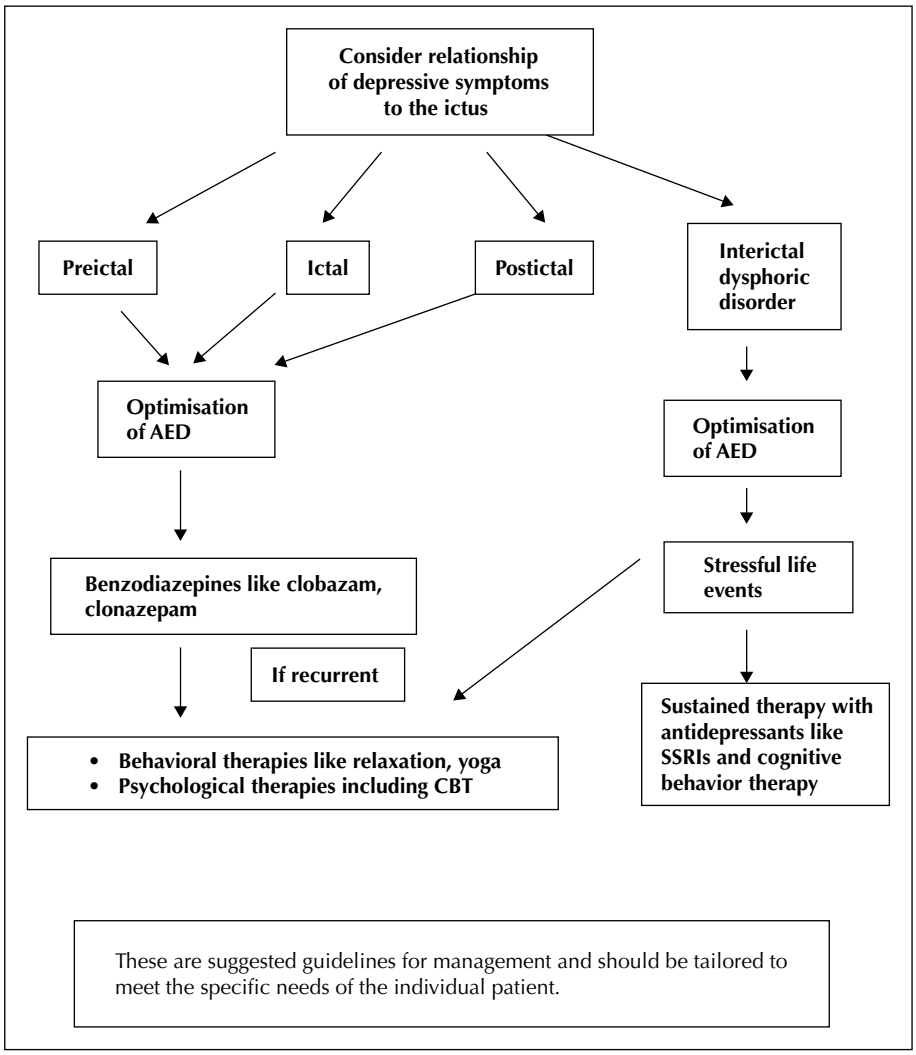

Figure 1. Management of epilepsy in depression.

resolution, as residual symptoms can impede the patient's quality of life *(figure 1)*.

Conclusion

Although most studies have reported a higher risk of depression in people with epilepsy as compared with normal controls, almost all studies (with a few exceptions such as Blumer 2002) report no difference between patients with epilepsy and other chronic disorders (Krishnamoorthy 2002). An argument raised by neuropsychiatrists and epileptologists is that patients with epilepsy have distinct and unique forms of psychopathology (Krishnamoorthy 2000, 2001). Neither traditional systems of classification used in psychiatry, such as the DSM or the ICD, which club the disorders under the broad umbrella of organic mental disorders, nor the ILAE classification, which does not address the psychiatric components of the disorder, do justice to these unique syndromes of "epilepsy-specific" psychopathology. The instruments used for identification of psychopathology in most studies are based on existing classification systems and are perhaps inadequate. Bear and Fedio (Bear and Fedio 1977) showed that while the MMPI failed to identify the difference between patients with TLE and other patient groups, the differences became apparent when the responses to an instrument they developed were analyzed. Blumer's description of the interictal dysphoric disorder, seen in patients with refractory temporal lobe epilepsy, further endorses the need for a distinct classification system enabling a clearer phenomenological description of psychopathology in these patients.

Diagnosis of depressive states can be difficult. Studies have found that hospital medical and nursing staff fail to detect affective disorders in 34-72% of cases (Mayou 1986), and that General Practitioners correctly diagnose depression at first consultation in only 50% of cases (Roberts 1995). In patients with epilepsy, this problem is further compounded due to the presence of unique depressive syndromes (Hesdorffer 2000). Identification of these variants becomes important from a public health perspective. An increased prevalence of psychiatric co-morbidity in patients with epilepsy as compared with other adequately matched illness groups would warrant the creation of specific mental health resources for this patient group.

Although the first reference to epilepsy and melancholia was made by Hippocrates in 400 BC, two thousand years later, neuropsychiatrists and epileptologists are still grappling with the nuances and challenges posed by this sacred disease. A mere 7% of neurologists treating epilepsy routinely screen for depression in their outpatient clinics (Gilliam *et al.* 2004). With the description of a six-fold increased risk of unprovoked seizures in older patients with major depression and the possibility of a reverse causality, the relationship between affective disorders and epilepsy becomes even more intriguing (Kanner 2003). Affective disorders in epilepsy classically exemplify the expanding interface between psychiatry and neurology, the mind-body conundrum. Is it not time that neurologists and psychiatrists start talking to one another (Kanner 2003)? □

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