

Emotional Concomitants of Epilepsy

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Psychiatric Disorders in Epilepsy

- Depression
- Anxiety Disorders
- Psychosis
- Personality Disorder
- Substance Abuse

Prevalence rates are difficult to estimate for these various disorders at the present time, as there have been no large community based surveys. Moreover, although studies have been completed in neurology clinics and psychiatric institutions, few studies have used reliable standardized measures of psychopathology.

Manchanda, R. (2002). Psychiatric disorders in epilepsy: Clinical aspects. Epilepsy and Behavior, 3, 39-45.

Prevalence estimates of psychiatric disturbance in epilepsy tend to range from 20 to 50%.

Estimates are higher for specialty clinics and lowest among community based samples.

(Manchanda, 2002)

A Variety of Factors can cause the Behavioral/Psychiatric Disturbances Associated with Epilepsy

- ictal seizure discharge/periictal state
- CNS pathology
- effects of antiepileptic drugs (AEDs)
- adverse psychosocial consequences of having epilepsy (reactive)
- unrelated co-existence
- cognitive and temperamental (personality) attributes

Behavioral/Psychiatric Disturbances Associated with Epilepsy Can Differ on the Basis of Their Temporal Relationship to the Patient's Seizures

- Ictal state - Behaviors/emotions that are direct expressions of the epileptic seizure.
- Periictal State (Pre- or Postictal) - Behaviors/emotions that are temporarily associated with seizures but are not direct manifestations of epileptic discharges.
- Interictal Period - Behaviors/emotions that are a function of non-ictal conditions.

Although there is general agreement that prevalence rates of psychiatric comorbidity are higher among epilepsy patients, the relationship between seizure type, seizure focus, and psychiatric status remains uncertain.

Psychosis in Epilepsy

Psychotic Disorders Appear to be Over-Represented in Epilepsy Patients, with prevalence estimates ranging from 2.5 to 8% as compared with a 1% rate among the general population.

- Trimble, M. R. (1991). The psychoses of epilepsy. New York: Raven Press.
- Blumer, D., Montouris, G., Hermann, B. (1995). Psychiatric morbidity in seizure patients on a neurodiagnostic monitoring unit. J Neuropsychiatry Clin Neurosci, 7, 445-456.

Ictal Psychosis

(Common Features)

- olfactory and gustatory hallucinations
- visual or auditory hallucinations (often involving poorly defined shapes or sounds, although there may be complex visual scenes or speech)
- paranoid or grandiose thoughts
- frontal or temporal automatisms
- tends to be a rare occurrence
- episodes of nonconvulsive status epilepticus can be mistaken for schizophrenia or a manic-like state.

Nonconvulsive partial status epilepticus can manifest as prolonged states of fear, mood changes, automatisms, or psychosis that resemble an acute schizophrenic or manic episode.

While usually confused, such patients may be able to perform simple behaviors and respond to commands and questions.

Marsh, L., & Rao, V. (2002). Psychiatric complications in patients with epilepsy: A review. *Epilepsy Research*, 49, 11-33.

Management of Ictal Psychosis

- Adequate seizure control with antiepileptic drugs or surgical procedures represents the optimal management of ictal psychosis.
- A careful review and verification of an epilepsy diagnosis as well as a thorough history of psychiatric disturbance can be of some help in distinguishing this ictal state from a pure psychiatric disturbance.
- However, confirmation by EEG recording is the most definitive way to confirm that this state is an ictal event (i.e., clinical indistinguishable from other psychotic states).

Interictal Psychosis - Some studies suggest that interictal psychosis looks a great deal like the hallucinations and delusions observed in schizophrenia, and have suggested a link to temporal lobe pathology.

- Slater & Beard, 1963: Noted that these patients had a relative absence of premorbid personal or familial psychopathology, although they had an increased prevalence of temporal lobe abnormality.
- Hill (1953) and Pond (1957) reported a relationship between temporal lobe epilepsy and a chronic paranoid hallucinatory state.

Perez, M. M., & Trimble, M. R. (1980). Epileptic psychosis: Diagnostic comparison with process schizophrenia. British Journal of Psychiatry, 137, 245-249.

- Reporting on 24 consecutive patients with epilepsy and psychosis, they noted that 50% of these patients presented with traits that were diagnostic of schizophrenia in the absence of organic features (Schneiderian first-rank symptoms of schizophrenia). All patients with Schneiderian symptoms had temporal lobe abnormalities. Patients with generalized epilepsy from this sample tended to have depressive or manic symptoms with psychosis but few or no Schneiderian symptoms.

Flor-Henry, P. (1969). Psychosis and temporal lobe epilepsy. Epilepsia, 10, 363-395.

- Flor-Henry felt that there is a relationship between the lateralization of the epileptic focus in patients with temporal lobe epilepsy and psychosis. He postulated that left- and right-sided seizure foci are more likely to be associated with a schizophrenia-like and manic-depressive presentation, respectively. Empirical support has been mixed.

Ring, H. A., Trimble, M. R., Costa, D. C., et al. (1994). Striatal dopamine receptor binding in epileptic psychosis. Biological Psychiatry, 35, 375-380.

- These researchers suggested that limbic pathology either produced by or associated with epilepsy is responsible for interictal psychosis, possibly due to modifications of dopaminergic pathways.

Postictal Psychosis

- Less well studied phenomena
- Appears to have a temporal relationship with seizure activity (i.e., patients emerge from the ictus in a confused state).
- Features include confusion, automatisms, wandering, delusions, hallucinations, and inappropriate behavior.
- When it occurs, postictal psychosis more frequently follows a flurry of complex partial seizures with or without secondary generalization or a single, prolonged seizure event.

Postictal Psychosis

- These symptoms remit within days or weeks, often without the need for neuroleptic treatment.
- However, in some patients the behavioral disturbance may be disruptive or prolonged, requiring pharmacological intervention (neuroleptics or benzodiazepines are typically used)
- Recurrence is common. Families of patients prone to postictal psychosis may learn to give a low-dose drug to prevent the precipitation of a postictal psychotic state.

- Logsdail, S. J., & Toone, B. K. (1988). Postictal psychosis: A clinical and phenomenological description. British Journal of Psychiatry, 152, 246-252.
- Savard, G., Andermann, F., Olivier, A., & Remillard, G. M. (1999). Post-ictal psychosis after partial complex seizures: A multiple case study. Epilepsia, 32, 225-231.

Depression in Epilepsy

A strong association between epilepsy and depression has been recognized throughout recorded medical history

Hippocrates noted in about 400 B.C. 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.”

Lewis, A. J. (1934). Melancholia: A historical review. Journal of Mental Science, 80, 1-42.

Galen (129-216 A.D.) wrote a treatise entitled *Epilepsy and Melancholy*, which emphasized that the main forms of both disorders arise in the brain and may have comparable underlying causes.

From: Gilliam, F., & Kanner, A. M. (2002). Treatment of depressive disorders in epilepsy patients. *Epilepsy and Behavior*, 3 (Suppl. 5), S2-S9.

Prevalence of Depression in Epilepsy

- “Depression is the most frequent psychiatric co-morbidity in epilepsy but very often remains unrecognized and untreated.”

Kanner, A. M., & Balabanov, A. (2002). Depression and epilepsy: How closely related are they? Neurology, 58 (Suppl. 5), S27-S39.

Published Prevalence Rates of Depression in Epilepsy

- Estimates of the occurrence of depression among patients with epilepsy range from 20 to 55% in patients with recurrent seizures and 3 to 9% in patients with controlled epilepsy.
- A study of concerns of patients living with epilepsy found that about one third of those surveyed spontaneously reported mood as a significant problem.

Gilliam, F., & Kanner, A. M. (2002). Treatment of depressive disorders in epilepsy patients. Epilepsy and Behavior, 3 (Suppl. 5), S2-S9.

Mendez, M. F., Cummings, J. L., & Benson, D. F. (1986). Depression in epilepsy. Significance and phenomenology. Archives of Neurology, 43, 766-770.

- Administered the Hamilton Depression Rating Scale to 175 consecutive patients in an outpatient epilepsy clinic and found that 55% met criteria for depression.

Jacoby, A., Baker, G. A., Steen, N., Potts, P., & Chadwick, D. W. (1996). The clinical course of epilepsy and its psychosocial correlates: Findings from a UK Community study. Epilepsia, 37, 148-161.

- In a community-based study that used the Hospital Anxiety and Depression Scale, these investigators found that 21% of 168 patients with recurrent seizures were depressed.

O'Donoghue, M. F., Goodridge, D. M., Redhead, K., Sander, J. W., & Duncan, J. S. (1999). Assessing the psychosocial consequences of epilepsy: A community-based study. British Journal of General Practice, 49, 211-214.

- These researchers examined a group of 155 patients identified through two large primary care practices in the UK using the Hospital Anxiety and Depression Scale. They found that 33% of those with recurrent seizures and 6% of those in remission had depression.

Although these studies have methodological limitations, they suggest that depression may be at least 3 to 10 times more prevalent in association with uncontrolled epilepsy than in the general population.

Epilepsy patients also appear to have a much greater risk of committing suicide than the general population

- Robertson (1997) reviewed 17 studies pertaining to mortality in epilepsy and suggested that suicide was nearly 10 times more frequent than in the general population (10 to 12 per 100,000). He suggested that this rate may be even higher when restricting the focus to only temporal lobe epilepsy.

Despite the increased risk for Depression and Suicide in epilepsy, mood disorders in this population often go unrecognized and/or untreated by practitioners

- Patients tend to minimize their psychiatric symptoms for fear of being further stigmatized.
- The clinical manifestations of certain types of depressive disorders in epilepsy differ from depressive disorders in non-epileptic patients and therefore go unrecognized by clinicians.
- Clinicians usually fail to inquire about psychiatric symptoms.

- Both patients and clinicians tend to minimize the significance of symptoms of depression because they consider them to be a reflection of a “normal adaptation process” to this chronic disease.
- The concern that antidepressant drugs (ADs) may lower the seizure threshold has generated among clinicians a certain reluctance to use psychotropic drugs in patients with epilepsy.

Kanner, A. M., & Balabanov, A. (2002). Depression and epilepsy: How closely related are they? Neurology, 58 (Suppl. 5), S27-S39.

Clinical Presentation of Depression in Epilepsy

Gilliam & Kanner (2002) suggest classifying depressive symptoms and disorders in epilepsy according to their temporal relation to seizure occurrence.

- Ictal Depression - Symptoms occurring as an expression of the actual seizure.
- Peri-ictal (Pre- or postictal) Depression - Symptoms occurring just prior to the onset of seizures or following their occurrence.
- Interictal Depression - Symptoms occurring that are unrelated to specific seizure episodes.

Ictal Depression

- This is the clinical expression of a simple partial seizure in which the symptoms of depression consist of its sole (or predominant) semiology.
- Psychiatric symptoms are thought to occur in approximately 25% of auras, with approximately 15% of these involving affect or mood changes.
- These spells are typically brief and stereotypical and occur out of context (without environmental precipitants), and are associated with other ictal phenomena.

(Gilliam & Kanner, 2002; Marsh & Rao, 2002)

Ictal Depression

- Laterality of the seizure focus does not have an apparent effect on the development of ictal depression (Devinsky & Bear, 1991).
- Ictal sadness may involve the features of typical interictal depressive syndromes, such as feelings of pathological guilt, hopelessness, worthlessness, profound despair, and suicidal ideation (Marsh & Rao, 2002).
- Patients may or may not recognize this reaction as out of line with their usual emotional state (Betts, 1991).

Preictal Depression

- This type of depression typically presents as a dysphoric mood preceding a seizure.
- Prodromal symptoms may extend for hours or even for 1 to 2 days prior to the onset of a seizure.
- These spells are typically brief and stereotypical and occur out of context, and are associated with other ictal phenomena.

Postictal Depression

- Postictal symptoms of depression have been recognized for a very long time, but their prevalence has yet to be scientifically established.

The real diagnostic/methodological challenge involves the classification of interictal depression.

Several investigators have noted that a large portion of epilepsy patients with depression do not fit the current DSM psychiatric syndromes

Clinical Presentation of Interictal Depression in Epilepsy

While patients with epilepsy can experience forms of depressive disorders identical to those encountered in nonepileptic patients, a review of the literature shows that a significant number of patients present with an atypical clinical presentation that fails to meet any of the DSM Axis I categories.

Gilliam, F., & Kanner, A. M. (2002). Treatment of depressive disorders in epilepsy patients. Epilepsy and Behavior, 3 (Suppl. 5), S2-S9.

Kanner, A. M., & Barry, J. J. (2001). Is the psychopathology of epilepsy different from that of nonepileptic patients? Epilepsy and Behavior, 2, 170-186.

Mendez, M. F., Doss, R. C., Taylor, J. L., & Salguero, P. (1993). Depression in epilepsy. Relationship to seizures and anticonvulsant therapy. J Nerv Ment Dis, 181, 444-447.

- Mendez et al. (1993) found that the depressive disorders of almost 50% of patients were classified as atypical depression according to DSM-III-R criteria.

Wiegartz, P., Seidenberg, M., Woodard, A., Gidal, B., & Hermann, B. (1999). Co-morbid psychiatric disorder in chronic epilepsy: Recognition and etiology of depression. Neurology, 53 (Suppl. 5), S3-S8.

- Wiegartz et al. (1999) found that depressive disorders of 25% of patients with epilepsy and depression were classified as depressive disorders not otherwise specified, according to DSM-IV criteria.

This problem with syndromal classification of depression in epilepsy has been noted by many other researchers, and has made the task of determining prevalence of this condition more difficult.

- Manchanda (2002) notes that most patients with epilepsy do not fit into the “Mood Disorders due to Epilepsy” or “Adjustment Disorder with Depressed Mood” categories of the DSM-IV. He feels that most will be classified as having an atypical depression, with a clinical picture of major depressive disorder being less common.

Patients experiencing depression in epilepsy often do not meet the criteria of major depressive disorder (i.e., their symptoms are less severe) but they also typically exhibit a more intermittent course than do patients with dysthymic disorder.

Barry, J. J., Lembke, A., & Huynh, N. (2001). Affective disorders in epilepsy. In Alan B. Ettinger and Andres M. Kanner (Eds.), Psychiatric issues in epilepsy (pp. 45-71). NY: Lippincott, Williams, and Wilkins.

Gilliam, F., & Kanner, A. M. (2002). Treatment of depressive disorders in epilepsy patients. Epilepsy and Behavior, 3 (Suppl. 5), S2-S9.

Kraepelin (1923) is credited with first describing an atypical syndrome of depression in epilepsy. Blumer (1997) more recently described this syndrome, giving it the name *interictal dysphoric disorder* (IDD). Blumer suggested that almost one third to one half of all patients with epilepsy seeking medical care suffer from this form of depression severely enough to warrant pharmacological treatment.

Kraepelin, E. (1923). psychiatrie (8th ed), Leipzig: Barth.

Blumer, D. (1997). Antidepressant and double antidepressant treatment for the affective disorder of epilepsy. J Clin Psychiatry, 58, 3-11.

Blumer (1997) feels that the symptoms of *interictal dysphoric disorder* have an intermittent course and can be categorized into depressive-somatoform and affective symptoms.

Interictal Dysphoric Disorder

Depressive-Somatiform Symptoms

- depressive mood
- anergia
- pain
- insomnia

Interictal Dysphoric Disorder

Affective Symptoms

- irritability
- brief euphoric states
- fear
- anxiety

Unfortunately, there are no current standardized diagnostic techniques for studying the proposed syndrome of interictal dysphoric disorder.

Nevertheless, evidence suggests that many epilepsy patients with depression do suffer from some form of “dysthmic-like” condition.

Bipolar Disorder in Epilepsy

- Few studies have formally examined the prevalence of bipolar disorder I and II in a rigorous, standardized fashion among patients with epilepsy, although there is some preliminary literature in this area.
- Many rating scales do not adequately assess symptoms of bipolar disorder.

Several case reports have reported an association between periictal mania in patients with epilepsy, typically with an epileptic focus in the nondominant hemisphere

- Barczak, P. (1988). Hypomania following complex partial seizures. British Journal of Psychiatry, 152, 572.
- O'Shea, B. (1988). Hypomania following complex partial seizures. British Journal of Psychiatry, 152, 571.
- Robertson, M. M. (1992). Affect and mood in epilepsy: An overview with a focus on depression. Acta Neurol Scand, 86, 127-135.

Summary of Research on Interictal Depression

- Depression occurs in patients with both uncontrolled and controlled epilepsy at a higher rate than the general population (although prevalence seems to be much higher for patients with uncontrolled seizures).
- Depression in epilepsy is often difficult to classify according to standard DSM Axis I syndromes (even when considering the “depression related to a known medical condition” category).
- While some patients will meet criteria for DSM syndromes (e.g., major depressive disorder, bipolar I and II, dysthmic disorder), many will present with a syndrome that seems to mimic a dysthmic disorder with a more variable, intermittent time course.

Summary of Research on Interictal Depression

- Some researchers and clinicians have suggested that an alternative classification system is necessary for this population (e.g., interictal dysphoric disorder).
- Prevalence literature in this area remains fairly muddy due to problems with a lack of agreement over the most appropriate classification system, differences in sampling (e.g., specialty clinic vs. community setting), wide-ranging practices of assessment (e.g., most often using patient self-report or clinician rating scales).

Typical Measures Used to Assess Mood and Personality in Epilepsy by Neuropsychologists

- Minnesota Multiphasic Personality Inventory
- Beck Depression Inventory
- Personality Assessment Inventory
- Various Quality of Life Measures

Typical Measures that Have Been Used to Screen For Depression in Epilepsy (By Physicians)

- Beck Depression Inventory
- Center for Epidemiologic Study Depression Screen
- General Health Questionnaire
- Medical Outcomes Study Depression Screen
- Primary Care Evaluation of Mental Disorders
- Symptom-Driven Diagnostic System - Primary Care
- Zung Self-Depression Scale

Additional Scales that Appear in the Research Literature or That Have Been Used in Various Drug Studies to Screen For Depression in Epilepsy

- Profile of Mood States
- Hamilton Depression Rating Scale
- Neurobehavioral Inventory
- Structured Psychiatric Interviews (these have been less frequently used but seem to be appearing more)

Direction of the Relationship Between Depression and Epilepsy

Forsgren, L., & Nystrom, L. (1990). An incident case referent study of epileptic seizures in adults. Epilepsy Research, 6, 66-81.

- These researchers found that depression was three times more common among patients with newly diagnosed adult-onset epilepsy than among controls.
- When their analyses focused on patients with partial seizure disorders, the history of depression was 17 times more common.

Hesdorffer, D. C., Hauser, W. A., Annegers, J. F. et al. (2002). Depression is a risk factor for seizures in older adults. Ann Neurology, 47, 246-249.

- These researchers found that epilepsy patients were 3.7 times more likely to have had a history of depression preceding their initial seizure as compared to controls.
- This finding was stronger for patients with partial epilepsy.
- These researchers concluded that the presence of depression may be an increased risk for epilepsy (i.e., the pathophysiology of depression may lower the seizure threshold).

Kanner (2002) suggests a possible bi-directional relationship between depression and epilepsy

He cites the previous research indicating that depression often precedes the onset of seizures.

He also notes that epilepsy seems to be a risk factor for depression (i.e., there seems to be a higher prevalence in epilepsy as compared to the general population).

It seems plausible that there is a common neuropathologic process that is contributing to the occurrence of both depression and epilepsy.

Of note, none of these studies examined cognitive changes, or explored where such alterations in functioning may fit into this sequence.

Etiology of Depression In Epilepsy

Kanner (2001) feels that depression in epilepsy can be related to three primary processes that can act independently or together in the presentation of the patient

- 1) An intrinsic epileptic process resulting from neurochemical and neurophysiologic changes in the limbic circuit.
- 2) An expression of the iatrogenic potential of many of the AEDs used in these patients.
- 3) An expression of a reactive process to a chronic disorder that requires multiple life adjustments.

Various causative factors have been *proposed* for the development of depression in people with epilepsy

Table 2. Etiology of depression in people with epilepsy

Neurologic (e.g., HI, MS, CVA, SOL)

Gender

IQ

Genetic/environmental factors

Endocrine/metabolic factors

Epilepsy Factors

Age at onset of epilepsy

Duration of Epilepsy

Seizure Type

Number of different seizure types

Localization of focus (LRE vs. PGE; TLE vs. extra-TLE)

Lateralization of focus

Seizure frequency

Seizure Severity

Seizure Control, “forced normalization”

Secondary generalization of seizure

Table 2. Etiology of depression in people with epilepsy (continued)

Iatrogenic

Type of AED

Number of AED

Serum level of AED

Secondary effects of AED, e.g., hormonal, serum folate deficiency

Effect of epilepsy surgery

Psychosocial

Stigma/Discrimination

Locus of control

Fear of seizures

Attributional style

Adjustment to epilepsy

Parental overprotection

Social support

Socioeconomic status

PWE, people with epilepsy; HI, head injury; MS, multiple sclerosis; CVA, cerebrovascular accident; SOL, space-occupying lesion; LRE, localization-related epilepsy; PGE, primary generalized epilepsy; TLE, temporal lobe epilepsy; AED, antiepileptic drug.

The cause of depression in an individual patient is likely multifactorial, with several contributing factors such as those found in the table compiled by Lambert and Robertson (1999).

What remains unclear is whether or not there are actually variables that consistently contribute to mood disturbance at the group level.

There are many studies supporting and refuting most of the factors in the list of possible causative factors. However, the vast majority of these studies are plagued by methodological limitations:

- Small sample sizes
- Limitations and variability in assessment methods
- Many studies have been retrospective in nature
- Use of Biased Samples (e.g., not including a mix of seizure types; sampling from different components of the epilepsy population)
- Failure to control for intervening variables and other possible causative factors (e.g., the impact of AEDs, psychosocial variables, other neurologic disorders/injury).

Currie, S., Heathfield, W., Henson, R., & Scott, D. (1971). Clinical course and prognosis of temporal lobe epilepsy: A survey of 666 patients. Brain, 94, 173-190.

- These researchers reported an elevated rate of depression and psychiatric disturbance among patients with TLE as compared to the general population.
- However, this study was basically a retrospective record review of epilepsy patients previously seen at London Hospital between 1949 and 1967.
- These researchers were able to interview about 1/2 of these patients. However, they were examining multiple variables (psychiatric issues is only one small component of the study), and it is not clear how they gathered information on psychiatric history.

Currie, S., Heathfield, W., Henson, R., & Scott, D. (1971). Clinical course and prognosis of temporal lobe epilepsy: A survey of 666 patients. Brain, 94, 173-190.

- They simply note that “all abnormalities of mental state were recorded except for those occurring immediately after operation” (130 had undergone epilepsy surgery). There is no mention of any standardized interviews or measures.
- They also did not control for the inclusion of patients with multiple etiologies that could impact both hemispheres of the brain (e.g., head injury, CNS infection) or that could cause depression in the absence of epilepsy (CVA).
- They actually found a much lower prevalence rate of depression than has been reported in other studies (perhaps due to their lack of a standardized assessment approach).

Table I. Methods of Follow Up

Seen Personally	374 (56%)
Contacted or Traced	99 (15%)
Neurosurgical Patients	130 (19.5%)
Untraced	63 (9.5%)

Problems: Almost 30% of this data came from records while another 15% came from retrospective interviews of family members.

Currie, S., Heathfield, W., Henson, R., & Scott, D. (1971). Clinical course and prognosis of temporal lobe epilepsy: A survey of 666 patients. Brain, 94, 173-190.

Table V. Psychiatric Aspects

<u>Mental State on Examination</u>	<u>No. of Patients</u>
Normal	375 (56%)
Anxious	127 (19%)
Depressed	71 (11%)
Aggressive	47 (7%)
Obsessive	41 (6%)
Severe Disturbance of Affect	38 (6%)

Currie, S., Heathfield, W., Henson, R., & Scott, D. (1971). Clinical course and prognosis of temporal lobe epilepsy: A survey of 666 patients. Brain, 94, 173-190.

Mendez, M. F., Cummings, J. L., & Benson, D. F. (1986). Depression in epilepsy. Significance and phenomenology. Archives of Neurology, 43, 766-770.

- This is another article that is frequently cited as demonstrating that depression is more associated with TLE, particularly with a left-sided foci.
- However, once again, multiple methodological problems makes drawing conclusions difficult.

- Part 1: Surveys were sent to patients presenting for vocational services for the disabled. Five hundred three epilepsy patients received questionnaires and 175 of these responded (35%). One hundred eighty-six patients without epilepsy were sent questionnaires and 70 (38%) responded.
- It is unclear from the article how the authors determined the seizure characteristics (or even the veracity of this diagnosis) for the epilepsy patients that they surveyed.

Mendez, M. F., Cummings, J. L., & Benson, D. F. (1986). Depression in epilepsy. Significance and phenomenology. Archives of Neurology, 43, 766-770.

- The 100-item survey included items from the Bear and Fedio Temporal Lobe Inventory and the Washington Psychosocial Seizure Inventory that were selected on face value (only 4 items specifically dealt with depression).
- The analyses involved comparisons of the two groups on single items from this scale.

Mendez, M. F., Cummings, J. L., & Benson, D. F. (1986). Depression in epilepsy. Significance and phenomenology. Archives of Neurology, 43, 766-770.

- Part II: Researchers identified all patients in a psychiatric facility who had a diagnosis of epilepsy in their records.
- They then compared 20 depressed patients with epilepsy to 20 depressed patients without epilepsy. All patients reportedly met DSM-III criteria for Major Depression.
- However, in the results section, it is stated that 2 had Bipolar Disorder, 2 had Schizophreniform disorder, 1 had Intermittent Explosive Disorder, and 1 had Alcoholic Hallucinations

Mendez, M. F., Cummings, J. L., & Benson, D. F. (1986). Depression in epilepsy. Significance and phenomenology. Archives of Neurology, 43, 766-770.

- AED history, AED blood levels, and EEGs were obtained on the study participants. (no description of this is provided)
- All patients underwent extensive interview, the Hamilton Depression Scale, and the Brief Psychiatric Rating Scale.
- More than half of the epilepsy patients presented with an agitated psychosis.

Mendez, M. F., Cummings, J. L., & Benson, D. F. (1986). Depression in epilepsy. Significance and phenomenology. Archives of Neurology, 43, 766-770.

- Fifteen of the 20 patients with epilepsy had focal discharges on EEG (Left = 10, Right = 1, bilateral = 4).
- Researchers concluded that a greater association exists between depressed mood and left TLE based on this pattern.

Mendez, M. F., Cummings, J. L., & Benson, D. F. (1986). Depression in epilepsy. Significance and phenomenology. Archives of Neurology, 43, 766-770.

Common Findings Regarding the Relationship of Depression to Seizure Variables in Epilepsy

Several recent reviews (Kanner, 2002) suggest that depression occurs more often among patients with complex partial seizures (particularly TLE) than among patients with primary generalized tonic-clonic seizures. Some also suggest a greater prevalence of depression in left TLE patients. However, these issues appear far from settled (Barry, Lembke, & Huynh, 2001).

Research Suggesting that Depression is More Common in Patients with Complex Partial Seizures

- Dongier, S. (1959-1960). Statistical study of clinical and electroencephalographic manifestations of 536 psychotic episodes occurring in 516 epileptics between clinical seizures. Epilepsia, 1, 117-142.
- Currie, S., Heathfield, W., Henson, R., & Scott, D. (1971). Clinical course and prognosis of temporal lobe epilepsy: A survey of 666 patients. Brain, 94, 173-190.
- Mendez, M. F., Cummings, J. L., & Benson, D. F. (1986). Depression in epilepsy. Significance and phenomenology. Archives of Neurology, 43, 766-770.
- Robertson, M. M., Trimble, M. R., & Townsend, H. R. A. (1987). Phenomenology of depression in epilepsy. Epilepsia, 28, 364-372.

Research That Found No Association Between Seizure Type and Depression In Epilepsy

- Kogeorgos, J., Fonagy, P., & Scott, D. F. (1986). Psychiatric symptom patterns of chronic epileptics attending a neurological clinic: A controlled investigation. British Journal of Psychiatry, 140, 236-243.
- Manchanda, R., Schaefer, B., McLachlan, R. S., & Blume, W. T. (1995). Relationship of site of seizure focus to psychiatric morbidity. Journal of Epilepsy, 8, 23-28.
- Dikmen, S., Hermann, B. P., Wilensky, A. J., & Rainwater, G. (1983). Validity of the Minnesota Multiphasic Personality Inventory (MMPI) to psychopathology in patients with epilepsy. J Nerv Ment Dis, 165, 237-254.

One interesting finding of several studies related to TLE patients, is that greater emotional maladjustment seems to result from the number of seizure types present in these individuals (i.e., patients with both complex partial seizures and GTCs tend to have poorer adjustment than patients with only one seizure type).

- Rodin, E. A., Katz, M., & Lennox, K. (1976). Differences between patients with temporal lobe seizures and those with other forms of epileptic attacks. Epilepsia, 14, 313-320.
- Hermann, B. P., Dikmen, S., & Wilensky, A. J. (1982). Increased psychopathology associated with multiple seizure types: Fact or artifact? Epilepsia, 23, 587-596.
- Dodrill, C. B. (1984). Number of seizure types in relation to emotional and psychosocial adjustment in epilepsy. In: R. J. Porter, A. A. Ward, Jr., and M. Dam (Eds), Advances in epileptology: XVth Epilepsy International Symposium, (pp. 541-544). NY: Raven Press.

Dodrill, C. B., & Batzel, L. W. (1986). Interictal behavioral features of patients with epilepsy. Epilepsia, 27 (Suppl 2): S64-S76.

- Dodrill and Batzel have argued that depression is more likely to occur as neurocognitive skills decline, since patients begin having greater difficulty meeting the demands of their environments. They found weak support for a relationship between greater cognitive dysfunction and heightened emotional maladjustment. Such findings tended to be greatest using tests designed on epilepsy patients (e.g., The Neuropsychological Battery for Epilepsy and the Washington Psychosocial Inventory versus the WAIS and the MMPI).

Research Suggesting that Depression is More Common in Patients with Left Temporal Lobe Epilepsy

- Altshuler, L. L., Devinsky, O., Post, R. M., & Theodore, W. (1990). Depression, anxiety, and temporal lobe epilepsy. Laterality of focus and symptoms. Archives of Neurology, 47, 284-288.
- Mendez, M. F., Cummings, J. L., & Benson, D. F. (1986). Depression in epilepsy. Significance and phenomenology. Archives of Neurology, 43, 766-770.
- Victoroff, J. I., Benson, F., Grafton, S. T., et al. (1994). Depression in complex partial seizures: Electroencephalography and cerebral metabolic correlates. Archives of Neurology, 51, 155-163.

Research Finding No Difference in the Prevalence of Depression Among Patients With Epilepsy of Left or Right Temporal Lobe Onset

- Mendez, M. F., Doss, R. C., Taylor, J. L., & Salguero, P. (1993). Depression in epilepsy. Relationship to seizures and anticonvulsant therapy. J Nerv Ment Dis, 181, 444-447.
- Hermann, B. P., & Wyler, A. R. (1989). Depression, locus of control, and the effects of epilepsy surgery. Epilepsia, 30, 332-338.
- Hermann, B. P., Seidenberg, M., Haltiner, A., et al. (1991). Mood state in unilateral temporal lobe epilepsy. Biological Psychiatry, 30, 1205-1218.

Mendez, M. F., Doss, R. C., Taylor, J. L., & Salguero, P. (1993). Depression in epilepsy. Relationship to seizures and anticonvulsant therapy. J Nerv Ment Dis, 181, 444-447. (Part I)

- Examined the medical records of patients with epilepsy or migraine headache referred to a neurology clinic between 1984 and 1992.
- Excluded patients with a history of neurological lesions on neuroimaging, craniotomy, specific epilepsy etiology, or background of closed head injury.
- Included patients with a documented history of psychiatric treatment. They used the DSM-III-R diagnosis that the patients had been assigned.
- They excluded patients with bipolar disorders without depressive symptoms and reactive depressive disorders.

Mendez, M. F., Doss, R. C., Taylor, J. L., & Salguero, P. (1993). Depression in epilepsy. Relationship to seizures and anticonvulsant therapy. J Nerv Ment Dis, 181, 444-447. (Part I)

- They found that 101 (7.5%) of 1339 epilepsy patients without manifest neurological lesions compared with 105 (5.3%) of 1991 migraine patients experienced depressive disorders.
- Diagnoses among epilepsy patients included: major depression (n = 25), bipolar disorders with depressive symptoms (n = 22), dysthymia (n = 4), and depression not otherwise specified (n = 50)
- There were no significant differences on laterality of focus.

Mendez, M. F., Doss, R. C., Taylor, J. L., & Salguro, P. (1993). Depression in epilepsy. Relationship to seizures and anticonvulsant therapy. J Nerv Ment Dis, 181, 444-447. (Part I)

- They acknowledge that they probably missed individuals who were depressed using this retrospective methodology with a reliance on formal psychiatric evaluation.
- They also recognized that migraine patients may not have comparable psychosocial problems.

Mendez, M. F., Doss, R. C., Taylor, J. L., & Salguero, P. (1993). Depression in epilepsy. Relationship to seizures and anticonvulsant therapy. J Nerv Ment Dis, 181, 444-447. (Part II)

- The authors examined the medical records and EEGs of the epilepsy patients with depressive disorders for 6 seizure variables: epilepsy type, average seizure frequency at last clinic presentation, presence of auras, EEG foci, anticonvulsant therapy at last clinic presentation, and epilepsy age of onset.
- They compared these patients on these variables with a group of randomly sampled epilepsy patients from the same clinic who did not have a depressive disorder.

Mendez, M. F., Doss, R. C., Taylor, J. L., & Salguero, P. (1993). Depression in epilepsy. Relationship to seizures and anticonvulsant therapy. J Nerv Ment Dis, 181, 444-447. (Part II)

- On seizure variables, fewer patients in the depression group had GTCS compared with non-depressed group.
- Depressed epilepsy patients with GTCs had fewer events than the non-depressed epilepsy patients with GTCs.
- The depressed patients had more AED polypharmacy than did their non-depressed counterparts.
- There were no differences on age of onset or seizure duration.

Some of the theories of the neural substrates of emotional processing may relate to the search for differences in mood expression based upon laterality of seizure foci.

- Some have suggested that the left hemisphere is responsible for positive emotional states and that the right hemisphere is responsible for negative emotional states. Seizure activity in one hemisphere might “release” the contralateral hemisphere.
- Others have suggested that non-dominant hemispheric activity may result in denial and neglect of negative emotions.

Drane, D. L., Holmes, M. D., Bachtler, S. D., & Dodrill, C. B. (2002). Differing emotional characteristics of patients with unilateral seizure onset as assessed with the Minnesota Multiphasic Personality Inventory (MMPI).

Epilepsia, 43 (Suppl. 7), 183.

- We analyzed the MMPIs completed during the pre-surgical evaluation of 99 epilepsy patients whose ictal and interictal EEG scalp recordings were lateralized to either the left ($\underline{n} = 57$) or right ($\underline{n} = 46$) frontal or temporal lobes.
- These patients were selected from a larger sample of pre-surgical epilepsy patients by excluding individuals with a history of neurologic disease or trauma thought to affect both cerebral hemispheres (e.g., head injury, encephalitis), and those who had experienced a stroke, as the latter condition has been shown to be related to depression and mania in some patients.

Drane, D. L., Holmes, M. D., Bachtler, S. D., & Dodrill, C. B. (2002). Differing emotional characteristics of patients with unilateral seizure onset as assessed with the Minnesota Multiphasic Personality Inventory (MMPI). *Epilepsia*, *43* (Suppl. 7), 183.

- Non-parametric tests showed that left and right hemisphere groups did not differ significantly in regards to age, gender, race, age at onset of seizures, intelligence, reading ability, or psychiatric history.
- Results of *t* statistics with appropriate corrections to guard against Type I error occurring due to multiple comparisons revealed that patient's with right unilateral onset had significantly higher hypomania scores (Scale 9: R onset: $M = 68.0$, $SD = 11.5$; L onset: $M = 60.3$, $SD = 11.5$) on the MMPI than did the left unilateral onset group ($t = -3.30$, $p < .001$).

Drane, D. L., Holmes, M. D., Bachtler, S. D., & Dodrill, C. B. (2002). Differing emotional characteristics of patients with unilateral seizure onset as assessed with the Minnesota Multiphasic Personality Inventory (MMPI). *Epilepsia*, *43* (Suppl. 7), 183.

- Both left and right seizure onset groups produced significantly elevated depression scores (Scale 2: R onset: $M = 70.2$, $SD = 9.0$; L onset: $M = 71.7$, $SD = 14.4$), but did not differ significantly from one another on this scale.

Drane, D. L., Holmes, M. D., Bachtler, S. D., & Dodrill, C. B. (2002). Differing emotional characteristics of patients with unilateral seizure onset as assessed with the Minnesota Multiphasic Personality Inventory (MMPI). *Epilepsia*, 43 (Suppl. 7), 183.

- After further dividing the original groups by regional cerebral onset (i.e., frontal vs. temporal), multiple analyses of variance were performed to look at regional differences. Results of these analyses revealed that these groups again differed on the hypomania scale ($F = 4.10, p < .009$).
- Post hoc analyses showed that the right temporal and right frontal groups both obtained significantly higher scores on this scale than did the left temporal group (Scale 9: RT: $M = 66.5, SD = 0.4$; RF: $M = 70.7, SD = 13.5$; LT: $M = 60.1, SD = 11.7$).
- In addition, the right frontal group scores significantly higher on this scale than did the right temporal group ($F = -4.18, p < .002$).
- The left frontal group was too small to draw significant conclusions about the performance of these patients.

Conclusions of Drane et al. MMPI study

- These results indicate that symptoms of depression are common in focal epilepsy patients with unilateral seizure onset regardless of side of focus whereas hypomanic symptoms seem to be more prevalent among epilepsy patients with right unilateral onset, particularly when seizures arise from the right frontal region.
- Elevated symptoms of hypomania observed in patients with right unilateral onset is consistent with lesional studies involving other patient groups (e.g., stroke) that have observed onset of mania after right-sided insults and case reports in epilepsy that have found an association between right-sided lesions and mania.
- These findings contribute to existing research suggesting that mood states may be associated with specific brain regions or neural networks, and that disruption of such regions may not require the presence of a frank lesion.

Neuroimaging Indicators of the Pathogenesis of Depression in Epilepsy

Most studies attempting to relate depression scores to neuroimaging data have found that lesions or functional abnormalities were associated with more severe symptoms of depression.

Quiske, A., Helmstaedter, C., Lux, S., & Elger, C. E. (2000). Depression in patients with temporal lobe epilepsy is related to mesial temporal sclerosis. Epilepsy Research, 39, 121-125.

- Quiske et al. (2000) assessed 60 patients with temporal lobe epilepsy using the Beck Depression Inventory and magnetic resonance imaging and found that patients with mesial temporal sclerosis had significantly higher depression scores than other patients.
- There was no difference in depression scores on the basis of seizure laterality.

Schmitz, E. B., Moriarty, J., Costa, D. C., Ring, H. A., Ell, P. J., & Trimble, M. R. (1997). Psychiatric profiles and patterns of cerebral blood flow in focal epilepsy: Interactions between depression, obsessionality, and perfusion related to the laterality of epilepsy. J Neurol Neurosurg Psychiatry, 62, 458-463.

- These investigators found that higher Beck Depression Inventory scores correlated with decreased temporal lobe and frontal lobe perfusion on ^{99m}Tc -HMPAO single photon emission computed tomography (SPECT) scans.
- No association was found between lateralization of the epileptogenic zone and depression.

Gilliam, F., Maton, B., Martin, R. C., et al. (2000). Extent of ^1H spectroscopy abnormalities independently predicts mood status and quality of life in temporal lobe epilepsy [abstract]. Epilepsia, 41 (Suppl.), 54.

- Gilliam et al. (2000) found a significant correlation between extent of ^1H magnetic resonance (MR) spectroscopy abnormalities in the temporal lobes and Profile of Mood States scores.
- Once again, no association was found between lateralization of the epileptogenic zone and depression.

Victoroff, J. I., Benson, F., Grafton, S. T., et al. (1994).
Depression in complex partial seizures:
Electroencephalography and cerebral metabolic correlates.
Archives of Neurology, 51, 155-163.

- Victoroff et al. (1994) examined 53 intractable epilepsy patients scheduled for surgery using standardized measures to assess for lifetime history of depression as well as current mood state.
- These measures included the Structured Clinical Interview for Diagnosis and the Hamilton Depression Rating Scale.
- They then used EEG telemetry and 18F PET scans to assess seizure laterality and frontal lobe hypometabolism.
- They found that left ictal onset was associated with a greater frequency of depression: 79% vs. 50% (nonsignificant).
- No correlation was found between current mood state and hypometabolism, but a history of depression was significantly correlated with left frontal lobe hypometabolism.

Neuroimaging studies of depression in epilepsy are consistent with increasing evidence that many psychiatric patients with depression have structural and functional neuroimaging abnormalities.

Sheline, Y. I., Wang, P. W., Gado, M. H., et al. (1996). Hippocampal atrophy in recurrent major depression. Proc Natl Acad Sci USA, 93, 3908-3913.

Sheline, Y. I., Sanghavi, M., Mintum, M. A., & Gado, M. H. (1999). Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. J Neurosci, 19, 5034-5043.

- Sheline et al. found that patients with a history of depression but no other neurological disease had smaller hippocampi than age-, sex-, and height-matched controls.
- They also found that core amygdala nuclei volumes correlated with hippocampal volumes.

Drevets, W. C., Price, J. L., Bardgett, M. E., et al. (2002). Glucose metabolism in the amygdala in depression: Relationship to diagnostic subtype and plasma cortisol levels. Pharmacol Biochem Behav, 71, 431-437.

- Other groups have found increased metabolism in the left amygdala using ^{18}F DG positron emission tomography (PET).

Drevets, W. C. (2001). Neuroimaging and neuropathological studies of depression: Implications for the cognitive-emotional features of mood disorders. Curr Opin Neurobiol, 11, 240-249.

- There has also been substantial evidence from neuroimaging and neuroanatomical studies of depression that the prefrontal and striatal systems play a role in the pathogenesis of depression as well.

Several studies have suggested that some metabolic abnormalities can normalize after effective pharmacological intervention or interpersonal therapies for depression.

Brody, A. L., Saxena, S., Stoessel, P., et al. (2001). Regional brain metabolic changes in patients with major depression treated with either paroxetine or interpersonal therapy: Preliminary findings. Archives of General Psychiatry, 58, 631-640.

Brody, A. L., Saxena, S., Mandelkern, M. A., et al. (2001). Brain metabolic changes associated with symptom factor improvement in major depressive disorder. Biol Psychiatry, 50, 171-178.

Neurotransmitter dysfunction in epilepsy and Depression: Is There A Common Link?

Epilepsy and depression may share common pathogenic mechanisms mediated by a decreased serotonergic, noradrenergic, dopaminergic, and gabaergic activity

(Kanner & Balabanov, 2002)

Schildkraut, J. J. (1965). The catecholamine hypothesis of affective disorders: A review of supporting evidence. American Journal of Psychiatry, 122, 509-522.

- Decreased serotonergic, noradrenergic, and GABAergic functions have been identified as pivotal pathogenic mechanisms of depression and have been the basis for antidepressant pharmacologic treatments.

Jobe, P. C., Dailey, J. W., & Wernicke, J. F. (1999). A noradrenergic and serotonergic hypothesis of the linkage between epilepsy and affective disorders. Critical Review of Neurobiology, 13, 317-356.

- Decreased activity of these same neurotransmitters has been shown to facilitate the kindling process of seizure foci, to exacerbate seizure severity, and to intensify seizure predisposition in some animal models of epilepsy.

The Impact of AEDs on Mood

Every AED, including those with positive psychotropic properties, can cause psychiatric symptoms in patients with epilepsy, some to a greater degree than others.

(Kanner & Balabanov, 2002)

Barbituates

- Associated with a significant risk of eliciting depressive symptomatology (Robertson, 1985).
- Should be avoided in patients with documented depression (Ettinger et al., 2002).
- Brent et al. (1987) showed that patients receiving phenobarbital as compared to carbamazepine demonstrated a statistically significant increased in the risk of depression and suicidal ideation in the former group, particularly among those with a personal or family history of affective disorder.
- May cause paradoxical hyperactivity, conduct problems, behavioral agitation, and irritability in children, adolescents, and patients with mental retardation (Ounsted, 1955; Wolf & Forsythe, 1978; Ferrari, Barabas, & Matthews, 1983; Corbett, Trimble, & Nicol, 1985; Stoudemire & Fogel, 1993).

Phenytoin (Dilantin)

- Some reports describe a relationship between phenytoin and depressive symptoms (Ettinger et al., 2002).
- Some individuals believe that this relationship may involve reactive symptoms from experiencing the stigma associated with the cosmetic side effects that can result from use of this AED.

Valproic Acid (Depakote)

- Commonly used as a mood stabilizer to treat Bipolar Disorder (Small et al., 1991; Freeman et al. (1992).
- May be useful in the treatment of panic and, possibly, of obsessive-compulsive disorder (Post et al., 1996).
- Agitation and mood problems in association with CNS neurologic abnormalities, such as head trauma or seizures, may be particularly responsive to valproic acid therapy (Stoll et al., 1994).
- Adverse effects include weight gain, gastrointestinal upset, hyperandrogenism, polycystic ovary disease, and neural tube defects in the offspring of pregnant patients (Knowles, 1999).
- In children with learning disabilities and complex partial seizures, VPA has been reported to induce or exacerbate hyperactivity and aggressive behavior (Husain & Wical, 1998).

Carbamazepine (Tegretol)

- Few studies cite negative behavioral effects associated with carbamazepine (Ettinger, Barr, & Solomon, 2002), and it has been demonstrated to have utility as a mood-stabilizer.
- Some studies have shown an exacerbation of behavioral problems in patients with pre-existing disturbances (Reid, Naylor, & Kay, 1981).
- Numerous reports suggest that carbamazepine may have utility in treating impulse control disorders, including borderline personality traits with aggression and dyscontrol syndromes (Silver, Yudofsky, Hurowitz, 1994).

Gabapentin (Neurontin)

- Several studies suggest that gabapentin contributes to an improved sense of wellbeing that is independent of seizure reduction (Dimond, Pande, Lamoreaux, & Pierce, 1996; Dodrill, Arnett, Hayes, et al., 1999; Harden, Lazar, Pick, et al., 1999).
- Open-label and case reports suggest that gabapentin has efficacy in treating mania (McElroy, Soutullo, Keck, & Kmetz, 1997; Knoll, Stegman, & Suppes, 1998), and the depressive phase of bipolar disorder (Young, Robb, Patelis-Siotis, et al., 1997; Ghaemi, Katzow, Desai, & Goodwin, 1997).
- Investigations are underway to study the impact of gabapentin in behavioral dyscontrol (Ryback & Ryback, 1995), agitation in senile dementia (Sheldon, Ancill, & Holliday, 1998), anxiety states (Pollack, Matthews, & Scott, 1998), social phobia (Pande, Davidson, Jefferson, et al., 1999), and self-injurious behaviors in neurologic syndromes (McManaman & Tam, 1999).

Gabapentin (Neurontin)

- Some patients with developmental disabilities may develop agitation (Ettinger, Barr, Solomon, 2002).
- There are also several reports that have cited the development or exacerbation of aggressive and agitated behaviors in epileptic children, most of whom had some degree of intellectual impairment (Wolf, Shinnar, Kang, et al., 1995; Lee, Steingard, Cesena, et al., 1996).

Lamotrigine (Lamictal)

- Epilepsy patients treated with lamotrigine have been shown to experience positive psychotropic effects, including improved quality of life scores (Meador & Baker, 1997).
- Lamotrigine is being used for treatment-resistant bipolar disorder (Kusumakar & Yatham, 1997; Kotler & Matar, 1998).

Lamotrigine (Lamictal)

- The effects of lamotrigine have been mixed in patients with developmental disabilities. For example, Beran and Gibson (1998) observed the development of aggressive or violent behavior (or both) in 14 of 19 developmentally delayed patients who received lamotrigine, while one patient demonstrated behavioral improvement. Ettinger et al. (1998) found that 3 of 20 mentally retarded epilepsy patients developed new or worsened hyperactivity, irritability, and stereotypy, while another four patients experienced positive psychotropic effects, including reduction in irritability and hyperactivity, decreased lethargy, diminished perseverative speech, or improvement in cooperation and better social engagement.

Tiagabine (Gabatril)

- One study of its use in treating intractable epilepsy patients demonstrated mood improvements that appeared to be independent of seizure control (Dodrill et al., 1998).
- Limited case series also note potential benefits against bipolar disorder (Kaufman, 1998).
- One study demonstrated improved mood and psychosocial adjustment when patients were switched from other AEDs to tiagabine monotherapy (Dodrill, Arnett, & Sommerville, 1997).

Vigabatrin (Sabril)

- Some studies have suggested a significant risk of inducing adverse psychiatric events, particularly psychosis. Patients at greater risk for such reactions seem to include those with severe epileptic disorders, a sudden reduction in seizure frequency, or a history of psychosis (Sander, Hart, Trimble, & Shorvon, 1991).
- Vigabatrin may exacerbate hyperkinesia in children with hyperactivity or static encephalopathy (Dulac, Chiron, Luna, et al., 1991; Appleton, 1993).
- Some favorable psychotropic reports are also available, such as utility in treating PTSD (Macleod, 1996).

Topiramate (Topamax)

- Some initial case reports suggest that topiramate may cause symptoms of depression in some patients, with some people suggesting that this may reflect a reaction to cognitive side effects (Shorvon, 1996; Betts, Smith, & Khan, 1997).
- A few reports indicated that topiramate may be useful in treating both the manic and depressive phases of bipolar disorder (Suppes, Brown, McElroy, et al., 1998; Sherman, 1999). An associated benefit has also been appetite suppression.

Association Between Depression and Poor Quality of Life in Epilepsy

Mood tends to account for a large portion of the variance in scores obtained on quality of life measures.

Perrine, K., Hermann, B. P., Meador, K. J. et al. (1995). The relationship of neuropsychological functioning to quality of life in epilepsy. Archives of Neurology, 52, 997-1003.

- Perrine et al. (1995) studied 257 epilepsy patients to determine the relationship of neuropsychological function to health-related quality of life (HRQOL).
- A mood factor score had the highest correlation of all neuropsychological variables with scales of the Quality of Life in Epilepsy Inventory-89 ($r = -0.20$ to $r = -0.73$ with the 17 subscales), and was the strongest predictor of quality of life in regression analyses.
- Forty-six percent of the variance in overall QOL was explained by the mood factor ($p < .0001$).

Lehrner, J., Kalchmayr, R., Serles, W., et al. (1999). Health-related quality of life (HRQOL), activity of daily living (ADL), and depressive mood disorder in temporal lobe epilepsy patients. Seizure, 8, 88-92.

- These investigators found that depression was the single strongest predictor for each domain of a German HRQOL measure, even after controlling for seizure frequency, seizure severity, and other psychosocial variables.

Gilliam, F., Kuzniecky, R., Meador, K., et al. (1999). Patient-oriented outcome assessment after temporal lobectomy for refractory epilepsy. Neurology, 53, 687-694.

- Gilliam et al. (1999) found that mood status was the strongest clinical predictor of the patient's assessment of their own health status in a group of 125 patients more than 1 year after temporal lobe surgery.
- Mood was the strongest predictor of one's subjective opinion of mental health, physical health, and role function (all separate factor scores).
- Other important predictors included employment status, driving ability, AED-free, and seizure-free status.

Little research has been completed to examine the efficacy of standard treatment interventions (pharmacological or psychotherapeutic) for depression in patients with epilepsy.

- Only one double-blind, placebo-controlled trial has been published to date that compared the use of antidepressant drugs (ADs) in epilepsy patients with depression. This study compared amitriptyline, mianserin (no longer available in the US), and placebo (Robertson & Trimble, 1985).
- The treatment of pre- and postictal depressive symptoms with ADs has not been evaluated, even in open trials.

Gilliam, R. A. (1990). Refractory epilepsy: An evaluation of psychological methods in outpatient management. Epilepsia, 31, 427-432.

- Gilliam reported that patients involved in psychotherapy not only showed significant improvement in rating scales of depression and anxiety but also showed a decline in seizure frequency.
- He suggests that the type of psychotherapy should be tailored to the needs of the individual, and might involve the inclusion of family members.
- It is thought that psychotherapy helps the patient deal more effectively with the stressors and limitations of living with epilepsy.

Gilliam and Kanner (2002) offer some suggestions regarding the use of AEDs for the treatment of depression in epilepsy

- Be sure that the onset of the depressive episode did not follow the discontinuation of an AED with mood stabilizing properties (e.g., depakote, lamotrigine). If it did, reintroduction of the AED or of another mood-stabilizing agent may be sufficient to achieve a normothymic state.
- Be sure that the onset of the depressive disorder did not follow the introduction of an AED with known negative psychotropic properties (e.g., phenobarbital, primidone, topiramate, vigabatrin). If so, lowering the dose or discontinuation of the new AED should result in symptom remission. In this second case, an AD may also be used to treat the suspected negative effects of the AED as well.

Gilliam and Kanner (2002) offer some suggestions regarding the use of ADs for the treatment of depression in epilepsy

- Start with low doses and make small incremental adjustments until the desired clinical response is reached to minimize the risk of causing and/or exacerbating seizures. They also add that this risk is low and should not deter the start of therapy.

Gilliam and Kanner (2002) suggest the use of SSRIs as the first-line treatment in depressed patients with epilepsy.

- Safe with respect to seizure propensity.
- Less likely to result in fatalities after an overdose.
- Possess a favorable adverse-effects profile.
- They have proven efficacy in dysthymic disorders with symptoms of irritability and poor frustration tolerance.

Gilliam and Kanner (2002) suggest the use of tricyclic antidepressants (TCAs) as a second-line treatment in depressed patients with epilepsy.

- Potential for cardiotoxic effects.
- Severe complications seen in cases of overdose.
- Blumer (1997, 2001) has anecdotal reports of the utility of low-dose TCAs in patients with epilepsy and interictal dysphoric disorder.

Many physicians have been cautious about the use of ADs to treat depression in epilepsy due to fears of lowering seizure thresholds, and thereby worsening seizure occurrence in these individuals.

Variables Associated with an Increased Risk of Seizure Occurrence Following Exposure to ADs in Nonepileptic Patients Include:

- High plasma serum concentrations
- Rapid dose increments
- The presence of other drugs with pro-convulsant properties
- the presence of CNS pathology, abnormal EEG, and personal and family history of epilepsy.

Anxiety in Epilepsy

Peri-ictal Anxiety

- Some patients pre-ictal anxiety states that can precede the seizure by several days (Blanchet & Fromer, 1986).
- Post-ictal anxiety and/or fear can last for hours or days (Paraiso & Devinsky, 1997).

Ictal Anxiety

- Fear and anxiety are fairly common ictal affects in patients with temporal lobe epilepsy (Williams, 1956).
- Some studies have linked these sensations with discharges of the anteromedial temporal lobe or structures of the limbic system (Penfield & Jasper, 1954; Gloor, Olivier, Quesney, et al., 1982).
- Usually the sensation is brief, lasting only seconds to a couple of minutes.
- Psychic phenomena, including hallucinations and feelings of déjà vu, jamais vu, and derealization and depersonalization, may be present (Scicutella, 2001).

Interictal Anxiety

- Anxiety syndromes appear to occur in both TLE and generalized epilepsy.
- Patients reportedly experience a variety of symptoms ranging from feelings of apprehension to DSM-IV syndromes (Panic Disorder, Generalized Anxiety Disorder, Obsessive-Compulsive Disorder).

SUMMARY

- Psychiatric syndromes often occur in patients with epilepsy at rates that seem to exceed the normal population.
- A lack of good prevalence studies makes it difficult to know whether or not prevalence rates of these syndromes exceeds that of other patient groups experiencing CNS dysfunction.
- Symptoms sometimes occur in association with seizures episodes (either ictally or peri-ictally), and such symptomatology tends to be brief and context-free.

SUMMARY

- Classic psychiatric syndromes tend to occur interictally.
- Depression appears to be the most common psychiatric feature in patients with epilepsy.
- Multiple factors likely contribute to depression in epilepsy (including psychosocial, neurologic, and treatment related variables). However, the relationship between most etiological factors remains uncertain despite hints at possible patterns.

SUMMARY

- Functional and structural neuroimaging suggests that severity of CNS pathology may be predictive of greater emotional distress.
- In addition, functional impairment may go well beyond the seizure ictus, with metabolic changes seen in multiple brain regions (e.g., bifrontal hypometabolism in depressed patients with TLE).
- Evidence of similar CNS pathology observed in depressed patients with no known history of neurologic disease also points to a relationship between mood disturbance and epilepsy (bi-directional?).

SUMMARY

- Functional and structural neuroimaging suggests that severity of CNS pathology may be predictive of greater emotional distress.
- In addition, functional impairment may go well beyond the seizure ictus, with metabolic changes seen in multiple brain regions (e.g., bifrontal hypometabolism in depressed patients with TLE).
- Evidence of similar CNS pathology observed in depressed patients with no known history of neurologic disease also points to a relationship between mood disturbance and epilepsy.

SUMMARY

- Greater cooperation is required between health-care disciplines to improve syndromal classification (e.g., “interictal dysphoric disorder”) as well as the measurement of symptoms (i.e., too many studies continue to use non-psychometric approaches and poorly validated instruments).
- A merging of technologies could be fruitful (i.e., the psychometric approach of neuropsychology and the promise of functional/structural neuroimaging).

SUMMARY

- Greater emphasis is required on developing treatment strategies specifically designed for the psychiatric (and cognitive) consequences of epilepsy.