ABSTRACT

Behavioral changes are common in epilepsy patients, with the overall spectrum of behavior in this population skewed toward cognitive impairment and psychopathology. Unfortunately, in many cases, the diagnosis is overlooked and therapeutic opportunities are missed. The pathogenesis of these disorders may include central nervous system pathology, ictal and interictal epileptiform activity, antiepileptic drugs, psychologic and environmental factors, and genetic predisposition. Although therapy for behavioral disorders is often deferred for fear of exacerbating epilepsy, treatment with psychopharmacologic agents is unlikely to increase seizure severity or frequency. Indeed, treating depression, anxiety, psychosis, and other disorders can improve sleep, reduce stress, and may even reduce seizure activity. Antiepileptic drugs have psychotropic properties that can be positive or negative and their effects may differ in epilepsy and purely psychiatric populations.


PSYCHIATRIC AND BEHAVIORAL DISORDERS IN EPILEPSY PATIENTS

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Psychiatric and behavioral changes are common among individuals with epilepsy. The potential causes for such changes as depression, anxiety, memory disorders, sleep disorders, and cognitive changes (Table) are diverse. The pathogenesis of epilepsy-related behavioral changes is discussed later in this article along with potential therapeutic approaches and the role of antiepileptic drugs (AEDs) in exacerbating or ameliorating these disorders.

The primary clinical problem in this emerging area is the lack of early recognition and diagnosis. In many cases, patients simply do not spontaneously report the problem. In other cases, the clinician and nurse fail to inquire about the patient's mental health. Chronic psychiatric symptoms are sometimes even misinterpreted as "a normal reaction" to having epilepsy.1 Certain patients, especially the elderly, will often deny feelings of depression or sadness when questioned about their mental state. Similarly, many physicians are too quick to deny that AEDs may contribute to behavioral problems, especially to the subtler types of cognitive or school performance problems.

Even if the symptoms are recognized, clinicians must realize that the epilepsy-related behavioral and cognitive changes will not always fit neatly into the standard psychiatric diagnostic categories (ie, the Diagnostic and Statistical Manual of Mental Disorders criteria). The development and evolution of negative behavioral problems such as psychosis, anxiety, depression, and memory impairment often follow a pathway distinct from that of patients with primary psychiatric illnesses. Beginning with publication of the classic...
studies of epilepsy and psychosis, for example, clinicians recognized the relatively preserved effect in these patients with epilepsy. While patients with epilepsy and interictal psychosis do share certain symptoms with the schizophrenic patient, they also differ in significant ways, not least of which is a lower chance of chronic hospitalization. More difficult to measure and compare with normal patients and other patient populations are the potential problems related to social interactions, personality issues, and comprehension of others’ emotions.

While the individual behavioral disorders related to epilepsy are still not fully characterized in this special population, the prevalence of these overlapping disorders is significantly higher in epilepsy patients. The affective disorders, anxiety, and psychotic disorders are probably the best described and most prevalent of the behavioral problems in epilepsy. Depression is one of the most common comorbid disorders, affecting about 3% to 9% of patients with controlled epilepsy and as many as half of those with recurrent seizures. Psychotic disorders occur in approximately 7% of the overall epilepsy population and in at least 10% of refractory groups. An estimated 5% to 20% of those with nonepileptic seizures also have a current or past history of epilepsy. Memory loss is consistently rated by patients with epilepsy as one of their top concerns, and long-term deficits are documented in about one third of all patients with temporal lobe epilepsy who undergo surgery. Other cognitive, sexual, social, and personality disorders are harder to measure but are more prevalent in those with epilepsy than in the general population.

**Pathogenesis and the Long-Term Impact of Seizures on Behavior**

The central nervous system pathologies that underlie epilepsy probably also contribute to the behavioral and psychiatric problems seen so often in the epileptic patient. These include all of the classic mechanisms suspected to play a role in seizures, including mesiotemporal sclerosis, gliotic changes, dysplasia, and channelopathies. In addition, overlapping these biomolecular and cellular pathophysilogies are several other disease-related contributory factors. These include use of AEDs, a broad range of psychological and environmental factors, and genetic predisposition. While the range of potential pathogenic factors obviously become impossible to distinguish in any single patient, they all seem to contribute to the higher rates of behavioral and cognitive dysfunction seen in the epileptic population.

A more clinically relevant way of considering pathogenesis involves the role of ictal and interictal activity. While most neurologists will admit that convulsive seizures lasting 30 minutes or longer and leading to oxygen deficit may indeed produce neuronal loss and long-term behavioral and cognitive deficits, many clinicians still feel that recurrent complex partial seizures or tonic-clonic seizures are not harmful. However, increasing evidence indicates that even the mildest of seizures types will have negative neuropsychological consequences over time. Even when magnetic resonance imaging is normal and the patient has never taken an AED, neuro-psych testing often detects memory loss or other cognitive or behavioral changes.

This was illustrated recently in a pediatric study involving one of the mildest forms of the disease: absence epilepsy. Researchers identified 65 patients (mean age at the time of interview, 23 years) who had been diagnosed with absence epilepsy over the previous decade. These patients participated in a structured interview that assessed a range of psychosocial function categories including academic-personal, behavioral, employment-financial, family, and social-personal relations. The

### Table. The Range of Behavioral Disorders in Patients with Epilepsy

- Affective
- Anxiety and obsessive-compulsive
- Psychotic
- Somatoform and dissociative
- Sexual (anorgasmia, impotence, low libido)
- Cognitive
  - Attention
  - Memory
  - Mental processing speed
  - Executive functions
- Social
- Personality
interview results were compared with those of a control group of patients with a juvenile rheumatoid arthritis (JRA)—children who presumably share chronic disease features such as stigma, pain, social issues, special medical requirements (often including hospitalization), and the need for medications. The results showed that the patients with absence seizures grew up to have marked differences in academic-personal and behavioral categories compared to the children with JRA ($P < .001$). Those with ongoing seizures had the worst outcomes.

Thus, even absence epilepsy, which many textbooks state will not impact behavior or cognition, may significantly alter the psychosocial outcomes of patients. Similar data on the association of benign Rolandic epilepsy and learning disorders, attentional disorders, and other pediatric problems are now being gathered. These studies are complex (e.g., needing to account for medications or disease severity), and the outcomes measured are often subtle, and results from larger and longer-term evaluations are definitely still needed. Yet, it already seems apparent from existing evidence that even the mildest forms of epilepsy may have long-term impacts on behavior and psychosocial outcomes in some patients.

**TREATMENT OF DEPRESSION, ANXIETY, AND PSYCHOSIS**

Psychotropic medications increasingly are given to patients with epilepsy who have behavioral problems. Key issues to consider when prescribing these psychotropic drugs include their effect on seizure threshold as well as their positive or negative impact on sleep time and efficiency. Clinicians must also be cautious about interactions with concomitant AEDs and, in particular, the possibility of augmented AED side effects. Several of these medications, especially the antipsychotics, may also directly affect cognitive or behavioral functions.

Researchers have evaluated the critical issue of seizure control during antidepressant therapy in epileptic patients. One study from the mid-1980s followed 59 patients with epilepsy who received low-to-moderate doses of antidepressants (mainly tricyclics). All patients had documentation of seizure frequency in the 2-month periods before and after initiation of psychotropic therapy. Overall, 59% of these patients had improved seizure control during therapy, 32% had unchanged rates, and only 12% worsened. Such results indicate that control of depression, probably by reducing stress and improving sleep, may actually reduce seizure frequency. Even if an antipsychotic medication marginally lowered the seizure threshold, the benefits in terms of reduced agitation and better sleep might act to reduce the seizure frequency.

In an updated version of that same study, researchers retrospectively assessed the impact of psychotropic medications (mainly selective serotonin reuptake inhibitors [SSRIs]) on seizure frequency in 57 patients with epilepsy. In this study, 33% of patients had fewer seizures, 44% were unchanged, and 23% worsened during the 3-month follow-up period. Overall, the mean seizure frequency did not significantly increase from the pretreatment period to the treatment period. Thus, these results with an array of modern psychotropic medications also support the conclusion that these drugs, if introduced slowly and used in low-to-moderate doses, can be safely employed in epilepsy patients with comorbid psychiatric pathology. The bottom line for clinicians is that epilepsy patients who are depressed or have other psychiatric disorders should be treated.

These study results are worth emphasizing because of the historical reluctance of physicians to use psychotropic medications for fear of lowering the seizure threshold. Some of this lingering reluctance can be traced to older psychotropic drugs such as chlorpromazine, unusually epileptogenic drugs such as clozapine, or misinterpretation of SSRI premarketing trials that rarely identify patients with a new-onset seizure—for example, over the typical 6- to 12-week follow-up periods, 1 of 3496 patients taking nefazadone and 1 of 2796 taking mirtazapine. These registration trials typically excluded any patient with a history of epilepsy, so even these low levels of seizures were seen by some as cause for concern. However, some preexisting cases may not have been recognized, and undiagnosed subclinical epileptiform activity occurs in approximately 1% of the general population. Therefore, the incidence of patients with new-onset seizures in these study populations receiving SSRIs should not raise significant concerns regarding SSRI use in epilepsy patients.

The possibility of worsened seizure control with psychotropic drugs is real and warrants monitoring in specific situations. Giving higher doses of SSRIs, for example, or targeting multiple brain receptors may increase the chances of provoking a seizure. Slow metabolizers of tricyclics may also need to have their dosage adjusted. Yet, worsening of seizures is not
common. Concern over making the patient worse should not prevent the clinician from providing anti-depressive therapy, which will very likely improve the patient's condition.

Anxiety disorders can also be treated effectively in the epilepsy population but the choice of agent can be critical. SSRIs are commonly used to treat anxiety disorders, and are discussed earlier in this section. These agents are safe in epilepsy patients if introduced slowly and used in low-to-moderate doses. Benzodiazepines typically provide excellent results over a short period (days to weeks) in anxious patients. Epilepsy patients, however, seem more susceptible than others to the problematic properties of benzodiazepines including tolerance and abuse, as well as anxiety and sleep disorders when they are withdrawn or when the dose is lowered. Long-term use of these agents can also cause cognitive (eg, impaired memory) and behavioral (eg, depression) problems. Reduction of the dose can increase seizure frequency or severity. Thus, although benzodiazepines are highly effective in some epileptic patients, long-term use in such patients may be problematic. In contrast, buspirone is usually effective and well tolerated in managing anxiety, and the SSRIs are also often effective at relatively low doses. Higher doses of SSRIs are typically required for obsessive-compulsive disorders and should be used with caution.

Postictal psychosis is another specific epilepsy-related disorder that deserves prompt, aggressive treatment. It typically occurs hours or days after a cluster of complex partial or tonic-clonic seizures. Early recognition is crucial and diagnosis can be hastened with careful interviewing of patients or their families—for example, asking about hallucinations or odd thoughts occurring in the hours or days after a seizure. Individuals with recurrent postictal psychosis (ie, 2 or 3 such episodes) may even be able to anticipate the onset and initiate treatment early or prophylactically. These postictal episodes can be treated with benzodiazepines or one of the other atypical antipsychotic drugs. For interictal psychosis, newer atypical antipsychotic medications are usually effective and well tolerated.

**Antiepileptic Drugs: Negative and Positive Psychotropic Effects**

All AEDs can have negative or positive psychotropic effects in different patients. Clinicians need to realize that these responses to AEDs are complex and idiosyncratic, especially in the pediatric population. The psychotropic effects of AEDs in patients with epilepsy may also differ markedly from those seen in the nonepileptic population, but the data are simply insufficient to draw any conclusions. For example, Lennox reported in the 1940s that phenobarbital not only controls seizures but also improves behavior and increases IQ in many patients. Reduced seizure frequency and intensity from effective therapy probably improved cognition, and was not a likely effect of phenobarbital. The greatest body of data for the psychotropic efficacy of AEDs is in bipolar disorder. Since this condition is relatively rare in patients with epilepsy, data supporting use of AEDs in the epilepsy population remain scant.

The negative psychotropic effects of AEDs may be underestimated. In many clinical settings, awareness of these adverse effects emerges only when the drug is withdrawn and when, for example, a child's performance in school or other social situations improves. Adverse neuropsychiatric events reported in placebo-controlled trials of AEDs include depression, decreased memory or attention, abnormal thinking, anxiety, somnolence, and insomnia. As indicated by this range of potential effects, the clinical response to any single AED can be heterogeneous and unpredictable. The danger with many of the common AED-associated negative effects (eg, fatigue or poor concentration) is that they may be considered part of the patient's underlying disease complex and therefore not confronted. Such an oversight is a missed opportunity to adjust dosage or to switch the AED in an effort to eliminate the drug side effect.

The potential positive psychotropic effects of this drug group are now increasingly recognized. Although solid double-blind evidence for the behavioral benefits of many of the AEDs is lacking, use of these agents by psychiatrists in nonepileptic populations has skyrocketed. Given the documented potential for negative effects with these agents, this increased off-label usage should be of concern.

One of the few truly well-established behavioral uses of AEDs is in mood stabilization or antimania treatment. For these indications, the efficacy of valproate and carbamazepine was documented in large randomized trials and, more recently, mood stabili-
lizing and antidepressive effects were documented for lamotrigine.\textsuperscript{14,15} There is also evidence of efficacy for gabapentin in social phobia.\textsuperscript{16} These instances, however, are the exceptions to the general rule that there is a paucity of data supporting use of AEDs for their behavioral effects; in fact, much of the double-blind data point to negative effects.\textsuperscript{10}

Still, many patients with psychiatric disorders do not respond to standard therapies, and that is why neuroactive alternatives such as the AEDs are so often employed. Actual support for use of AEDs in some of these other behavioral uses is based mainly on smaller series, unblinded studies, or case reports. Practically all of the AEDs have had some success in mood stabilization, and others have been employed in more specific settings, including gabapentin in generalized anxiety disorder, lamotrigine in depression, and topiramate in binge eating. Better studies of the positive and negative behavioral effects of AEDs are warranted.

**CONCLUSION**

Psychiatric and behavioral disorders are common, but often disguised, in patients with epilepsy. Early diagnosis of these disorders is key for effective therapy. Many behavioral changes do not fit neatly into the psychiatric nomenclature, yet may still be seriously disabling (eg, impaired social-emotional learning). Thus, clinicians must probe deeply to identify cognitive impairments and psychopathology in their patients with epilepsy. Above all, clinicians must not be overly concerned that treatment of behavioral disorders will exacerbate the epilepsy. Most evidence shows that treatment with psychopharmacologic agents is unlikely to increase seizure severity or frequency. The morbidity related to the behavioral disorders in epilepsy is significant and often more problematic than the epilepsy itself. Thus, treatment is critical.

**REFERENCES**