

Mood and Cognition Problems in Epilepsy: Are Antiepileptic Medications Really to Blame?

By: Nicole R. Villemarette-Pittman, PhD



Physicians encounter complaints about mood changes and cognitive problems from persons diagnosed with epilepsy every day. Antiepileptic drugs (AEDs) often receive the blame for these complaints and the logical next step is to try a new AED. However, the causes of these mood and cognition problems are likely the result of a combination of factors; and

thus, may not be fully alleviated by switching to a new AED. Three main reasons for mood and cognition problems or changes in persons with epilepsy include the basic pathology of the disease, side effects from AEDs and the cumulative social and occupational effects of recurrent seizures.

The exact cause of the epilepsy may provide expectations regarding the prognosis for cognitive and psychological development, especially those related to developmental defects and birth injuries. However, the location in the brain where the seizures start can provide substantial information as well. For example, temporal lobe epilepsies typically have a focused pathology with extensive connections to the limbic structures of the brain which are associated with emotion and learning. It would be anticipated that chronic disruptions in these pathways may lead to problems with learning, memory and mood.

These neural pathways and their neurotransmitter systems, including those important in behavior and memory (e.g. GABA, glutamate), are also the targets for AEDs. Many AEDs work on multiple neurotransmitter systems and can affect large portions of the brain, including areas that are not necessarily involved in the start of a seizure. AEDs can be effective at preventing or stopping epileptic activity in the brain, but they can also cause unwanted side effects.

The chronic disruptions in brain activity caused by seizures produce long-term effects, some of which have been well-documented by researchers. Overall, the duration of epilepsy, seizure type and seizure frequency play powerful roles in the behavior and intellect of persons diagnosed with epilepsy. Onset of epilepsy in childhood is associated with progressive, reduced intellectual and memory function.^{1,2} Persons experiencing generalized seizures perform poorer on Intelligence testing than those experiencing partial seizures;³ however partial seizures may have more pronounced effects on very specific tasks. For example, persons with right temporal lobe epilepsy demonstrate difficulties in non-verbal and visual-spatial tasks; whereas persons with left temporal lobe epilepsy may exhibit difficulties with verbal learning and memory.^{4,5,6,7} Persons who have high levels of interictal activity (sub-clinical, seizure-like activity seen on their EEG) suffer from frequent lapses in attention which may make learning difficult. These problems maintaining attention may be mistaken for AED side effects or even another ill-

ness, such as ADHD.

Epilepsy developed secondary to another problem, such as stroke, head trauma or Alzheimer's disease, is also associated with cognitive decline; although in some cases, the disease state itself is likely responsible for both the seizure activity and the cognitive decline. Persons with Alzheimer's disease have an increased risk for developing seizures⁸, but progressive cognitive decline would be expected regardless. New-onset seizures after stroke negatively effect cognitive functioning⁹ and promote vascular cognitive impairment¹⁰, which may then be exacerbated by AED polypharmacy. AEDs may worsen pre-existing cognitive weaknesses, even causing a complaint that starts out as bothersome to grow to a level of intensity that interferes with daily functioning. The normal aging process causes decline in some cognitive functions, such as reaction time and memory; and these normal, small declines in function can be magnified by AEDs in elderly persons regardless of their epilepsy etiology.

Cognition is not the only system that suffers acute and long-term effects from epilepsy. Long-term effects of recurrent seizures can include lower education levels due to sickness and lack of independence. Lower educational levels, coupled with occupational limitations due to safety and health-related absences, may result in lower paying jobs, more unskilled work and a higher rate of unemployment among epilepsy patients.¹¹ The social influences of long-term fear of embarrassment, reduced independence (e.g. no driving privileges) and social immaturity can also increase the likelihood of anxiety and depression.

Persons experiencing seizures have greater rates of depression and anxiety than the non-epileptic population. Over one-third of community-based epilepsy patients experience severe depression¹² and nearly one-third of epilepsy patients in tertiary care settings experience anxiety disorders.¹³ Individuals who have more frequent seizures have higher rates of depression and anxiety.¹⁴ As with cognitive side effects, polypharmacy increases the risk of anxiety and depression¹⁵ and epilepsy developed secondary to head trauma increases the risk of behavioral and personality problems.¹⁶

When a person with epilepsy complains of cognitive or mood problems, it is important to consider their age, pre-existing conditions, brain pathology, duration of epilepsy, seizure type and seizure frequency before prescribing a new AED or switching from an AED with good seizure control because of possible side effects. Some general guidelines to follow include:

Overall, old AEDs have more cognitive and mood effects than the new AEDs. Using more than one AED at a time increases the chances for negative cognitive outcomes. Any AED at high doses may effect cognition and behavior. Common AEDs that report the possibility for problems with attention, memory and concentration are benzodiazepines (e.g. clonazepam), carbamazepine, lamotrigine, phenobarbital, phenytoin, pregabalin,

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The Protein ADK Links Epilepsy

The brain of individuals who suffer from epilepsy is characterized by astrogliosis, a brain pathology evidenced by a complex series of changes in the morphology and function of brain cells known as astrocytes. Little is known about how astrogliosis relates to the dysfunction of brain cells known as neurons in individuals with epilepsy, but filling in the blanks in our knowledge could lead to new possibilities for therapeutic intervention. A study using mice by Detlev Boison and colleagues at Legacy Clinical Research, Portland, has now identified the protein ADK in astro-

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FOUNDATION NEWS

MESSAGE FROM THE DIRECTOR:

Thanks for all of the hard work that has been on-going with and for the Foundation and all people with epilepsy in Louisiana. Parent's Against Childhood Epilepsy (PACE), gave the Foundation a \$25,000 grant to support existing services and summer camp for youth-THANKS AGAIN, PACE! A big thank you goes out to UCB Pharma, Inc. for its support of the upcoming race in Baton Rouge and the Huey and Angelina Wilson Foundation for its challenge match grant. Staff are working diligently on new projects. Look forward to a new golf tournament in North Louisiana in March, the huge Epilepsy Walk in Baton Rouge in April, and our new on-line fund raising services. Simply by clicking onto goodsearch.com you can support us by designating to the Foundation through Yahoo.

Regarding client services, it is imperative that all of you contact the Board of Pharmacy at 225-925-6496 to report any problems you may have had with epilepsy medicine that was switched to a generic without you or your doctor's approval. We will be trying to pass legislation this in April to ensure that switches of medicine do not occur without you and your doctor's approval. Call us if you have questions at 800-960-0587.

Welcome to our new staffers, Karen Marchand and Amy Nichols. Karen is in charge of advocacy services and Amy is handling N. Louisiana services. Both are extremely qualified and motivated to make a difference for people with epilepsy in Louisiana. Remember, together we can work so that "NOT ANOTHER MOMENT IS LOST TO SEIZURES".



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Join us Saturday, April 26th for our 4th Annual Seize the Day 5K Run/Walk

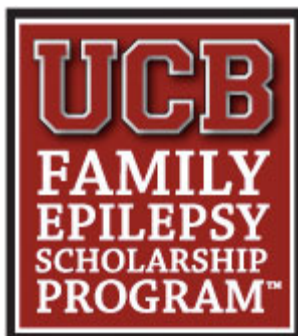
Raise the most money and win a cruise for 2!

Visit our website at www.epilepsyloouisiana.org and click on the Seize the Day Website

or call us at: 800-960-0587

or email us at info@epilepsyloouisiana.org

UCB, Inc. will award 30 one-time scholarships in 2008



People with epilepsy, their family members, or caregivers of people with epilepsy are encouraged to apply for the UCB Family Epilepsy Scholarship Program. UCB will award thirty one-time scholarships this year to as follows:

- Twenty \$5,000.00 scholarships to people with epilepsy and
- Ten \$5,000.00 scholarships to family members or caregivers of people with epilepsy.
- To download a copy of the scholarship application, go to www.UCBScholarship.com.

The completed application must be postmarked by **May 2, 2008**. Scholarship winners will be notified in August. For more information visit our website www.epilepsyloouisiana.org.

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primidone, tiagabine, topiramate and zonisamide. Common AEDs that report the possibility for problems with mood, depression, anxiety and irritability include benzodiazepines (e.g. clonazepam), ethosuximide, felbamate, gabapentin (in children), levetiracetam, phenobarbital, phenytoin, pregabalin, primidone, tiagabine, topiramate and zonisamide.

AEDs that are relatively neutral with respect to cognition are gabapentin, levetiracetam, oxcarbazepine and valproate. AEDs that may benefit mood include carbamazepine, gabapentin, lamotrigine (also indicated for Bipolar Disorder), oxcarbazepine and valproate.¹⁷

When reviewing AED choices for treatment, if access to medication is a problem, then an older, less expensive AED may need to be considered. Valproate may be a good first choice due to its low cost, seizure type indication (partial and generalized) and minimal cognitive side effects. For persons with a history of mood problems, oxcarbazepine may be an appropriate first choice. For adjunctive therapy, especially in persons taking medications for other illnesses, levetiracetam may be a good second AED. It has minimal effects on cognition and a relatively clear drug interaction profile.

In general, older, sedating AEDs with multiple side effects should not be a first-choice drug. For example, phenobarbital can cause a variety of central nervous system effects (e.g. sleep or appetite changes) which can then initiate or exacerbate cognitive or behavior problems, in addition to this drug's direct effects on cognition and mood. Phenobarbital can also cause negative reactions when paired with another AED, such as valproate. That is not to say that these drugs do not have a benefit, however their introduction in treatment should be considered after drugs with a more neutral side effect profile have been tried.

In summary, AEDs can cause cognitive and behavioral side effects, especially when taken in combination with other medications and in high doses. However, many other factors contribute to similar complaints. Some are the result of the long-term effects of having epilepsy and may not be alleviated by switching to another AED. Some are the result of a primary illness or trauma and a medication change may or may not help. When a clear time course, medical history and social history point toward the direct effects of an AED, review the advantages and disadvantages of the available medications before selecting the next one to try. If an AED or combination of AEDs results in seizure freedom, give extra weight to the seizure control factor in the equation and try a dose modulation to alleviate side effects before an actual medication change. In many cases, the seizures themselves will produce more harm than a bothersome medication side effect.

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cytes as a molecular link between astrogliosis and neuronal dysfunction in epilepsy.

The authors observed in a mouse model of epilepsy that ADK upregulation and spontaneous seizures occurred in the region of the brain affected by astrogliosis. In addition, overexpression of ADK in a specific region of the brain triggered seizures in the absence of astrogliosis. Conversely, mice engineered to express less ADK in specific regions of the brain were protected from chemical-induced epilepsy. Furthermore, as ADK-deficient ES cell "derived implants protected normal mice from chemical-induced astrogliosis, ADK upregulation, and seizures, it was suggested that ADK-based treatment strategies might provide a new approach for the treatment of individuals with epilepsy.

Article adapted by Medical News Today from original press release.

Early Treatment Stops Epilepsy in its Tracks

Yale School of Medicine researchers have shown for the first time that it is possible to suppress the development of epilepsy in genetically predisposed animals-which could open the door to treating epilepsy as a preventable disease.

According to the study published this month in *Epilepsia*, early treatment of epilepsy-prone rats with the anti-convulsant medication ethosuximide before the onset of seizures led to a marked suppression of seizures both later in life and months after treatment stopped.

"Current treatments for epilepsy may control seizures, but they do nothing to alter the underlying disease," said [Hal Blumenfeld, M.D.](#), associate professor of [neurology](#) and lead author of the study. "These findings are important because they set the stage for prevention of epilepsy in genetically susceptible people."

Epilepsy is a common neurological disorder that affects about 50 million people worldwide. It is characterized by seizures-temporary loss of consciousness or muscular control-that are precipitated by abnormal electrical overload on neurons within the brain.

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PARTICIPATE IN EPILEPSY RESEARCH

Depression & Epilepsy

If you are 18-65 and have been diagnosed with temporal lobe epilepsy and major depressive disorder then you may be eligible to participate in a clinical research trial being conducted by Dr. Erich Conrad at the LSU Health Sciences Center Anxiety & Mood Disorders Clinic. To learn more about this study, please call (504) 897-8559. Study participants will receive investigational study drug or placebo and study related tests at no cost. Compensation for time and travel may be available. Call the LSUHSC Anxiety & Mood Disorders Clinic at (504) 897-8559

Lacosamide Monotherapy Trial for Partial Seizures

Schwarz Biosciences is sponsoring a multi-site clinical trial for persons 16 to 70 years with a diagnosis of partial seizures. Persons who meet the study criteria and are willing to participate will receive either 300 mg per day or 400 mg per day of Lacosamide for up to 20 weeks with a potential option to enter an open-label trial. Study visits and study medication costs will be covered by the Sponsor (Schwarz). Persons interested in getting more detailed study information should e-mail the study coordinator for the LSU Epilepsy Center of Excellence in New Orleans at epicenter@lsuhsc.edu. Please provide your name, e-mail address or telephone number and the study in which you are interested.

Lexapro Study for Depression in

Persons with Temporal Lobe Epilepsy

Forest Pharmaceuticals is sponsoring a clinical trial at the LSU Behavioral Sciences Clinic in New Orleans for persons who are 18 to 65 years of age with temporal lobe epilepsy and suffer from depression. Persons who meet the study criteria and are willing to participate will receive Lexapro for 10 weeks. Study visits and study medication costs will be covered by the Sponsor. Persons interested in getting more detailed study information should e-mail the study coordinator at epicenter@lsuhsc.edu. Please provide your name, e-mail address or telephone number and the study in which you are interested.

Teen Outreach Hits Homes



By: Holly Guess, EFLA Staff

"I was kind of scared and nervous at first". This is how Abby Perrault says she reacted when she was first diagnosed with epilepsy. You would never know by meeting her. It was truly a pleasure for me to meet Abby and her family. She has a great outlook on living with epilepsy and has one of the most

fun and energetic personality of any eleven year old I know. Abby suffers from Absence seizures and says during a seizure, "I blank out and can't hear anything. I just kind of stare off and my lips move. After the seizure, I realize that I just had one".

Abby's story is truly a testament to the work the Foundation does. Every year we go into various schools throughout the state and educate teens on epilepsy and seizure first aid. Every year this program educates hundreds of middle and high school students. St. Joseph's Academy (SJA) in Baton Rouge faithfully participates in this program and requires their incoming freshman to take part in learning about epilepsy and proper first aid. This year at SJA we had the pleasure of meeting Mary Margaret Perrault. After hearing one of our epilepsy educators speak about epilepsy and the different types of seizures, Mary Margaret telephoned her mother to say that she knew what was wrong with her sister Abby; she thought Abby was having seizures. Amy and Steven Perrault, Abby's parents, said they felt something was going on with Abby although they weren't sure what was happening and kept putting off making an appointment. After Mary Margaret called, Amy said she knew she had to make an appointment with a neurologist. Abby saw Dr. Charlotte Hollman in Baton Rouge who confirmed what Mary Margaret thought- that Abby had epilepsy. Abby was scheduled for a sleep deprived EEG. Since lack of sleep is a seizure trigger, it is hoped that this type of EEG will trigger a seizure and

make it easier to pinpoint where in the brain seizures are originating. Abby and her dad stayed up all night preparing for the test. Abby had multiple seizures during her EEG and Dr. Hollman was able to confirm that Abby was having seizures. Abby says that she is not sure if anything triggers her seizures but, "the doctor told me that bright, blinking lights can trigger a seizure."

Abby says that having epilepsy does not prevent her from doing anything. Abby takes Lamictal and says that she feels she is having fewer seizures, but is still having them. "I have only been on the medication for a month and a half. I can't really say how many seizures I have in a current month. I have a few a day - it's never over 10 though." Abby is a fifth grader at St. Thomas Moore Catholic School



Abby, Mary Margaret, & Emma Perrault

in Baton Rouge and says her friends don't mind that she has epilepsy. I asked Abby what she would like people to know about epilepsy and she said, "that there are different types and it's not always bad." I also asked Abby what she would like people to know about her and she said, "that I'm cute". Abby said that the hardest thing about living with epilepsy is that, "people don't understand what epilepsy is".

Abby's story is a true testament to why epilepsy awareness is so important. Epilepsy is the most common neurological condition in children; with more than 326,000 affected. Children with absence seizures are often misdiagnosed as having ADD or just not paying attention, but through epilepsy education and community awareness we can ensure that *Not Another Moment will be Lost to Seizures*.



Abby's artwork titled "Up All Night" which she did while preparing for her sleep deprived EEG.

For more information on how your business, school, or organization can participate in epilepsy education call our office at 800-960-0587 or email us at

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Using a combination of molecular profiling, electroencephalogram (EEG) recordings, and power spectral analysis, Blumenfeld and his colleagues demonstrated that ethosuximide effectively blocked the expression of an epilepsy-associated maladaptive protein within neurons of the brain and reduced the number of seizures in treated animals.

"These findings prove that prevention of epilepsy in people is an achievable goal," Blumenfeld said. "Strategies for primary prevention of diseases like epilepsy will be increasingly important as genetic prediction of these diseases improves."

He said the results must be confirmed in other animals and with other medications before moving on to human treatment trials.

Support Groups Around the State

New Orleans

7:00 p.m. - 8:00 p.m.
Third Thursday of the month
St. Frances Xavier Parish Center
444 Metairie Road, Metairie.

Baton Rouge

7:00 p.m.— 8:30p.m.
Third Thursday of the month
10101 Park Rowe Circle
Baton Rouge

Shreveport

Christus Schumpert
One St. Mary Place
Visit our website for dates
and times

Reach any of our offices at: **800-960-0587**

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Our Mission

The Epilepsy Foundation of Louisiana will ensure that people with seizures are able to participate in all life experiences; and will prevent, control and cure epilepsy through services, education, advocacy and research. The Epilepsy Foundation is a not-for-profit, volunteer health agency and an affiliate of the national Epilepsy Foundation.

Disclaimer: *The information in this newsletter is for informational purposes only, and should NOT be construed as any type of medical or legal advice or treatment. The Epilepsy Foundation of Louisiana does not recommend any one product, treatment, or trial. All cases of epilepsy are different and only a certified physician can properly treat any given individual.*