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# Epilepsy and mood

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**WHAT WAS THE STUDY ABOUT?** In their article, "Use of antiepileptic drugs in epilepsy and the risk of self-harm or suicidal behavior," Dr. Andersohn and his coauthors[1] tried to better understand a very difficult problem. For years, it has been known that there is a higher rate of suicide in people with epilepsy. People with epilepsy are also more likely to have depression, which can lead to suicide. In addition, some of the medications that are used for seizures (also called antiepileptic drugs or AEDs) may cause problems with mood. Because all of these problems overlap, it can be difficult to sort out how they are related.

In early 2008, the United States Food and Drug Administration (FDA) issued a safety alert concerning all AEDs. The alert was based on 199 studies. In these studies, an antiepileptic medication was compared to placebo. A placebo is a fake medication to see if the actual medication works. When grouped together, the analysis showed that there was an increased risk of suicidal thoughts and behavior in people who were taking an AED.

The FDA analysis grouped all seizure medications together. It was not possible, based on the information that they had, to decide if there were specific medications that were more likely to cause mood problems. Dr. Andersohn and his coauthors decided to answer this question, if possible. What they wanted to know was simple: Are there certain medications that cause this more often than others?

**HOW WAS THE STUDY DONE?** Dr. Andersohn and his coauthors wanted to gather as much information as possible on these medications. To do this, they used a database of medical information. The database has been in place in the United Kingdom for several years. It is called the General Practice Research Database. The information is gathered in an anonymous way to protect patients. The information is submitted by medical experts from 450 general medical practices in the United Kingdom. The information is collected over time and there are now more than 6 million people in the database.

Of the more than 6 million people, Dr. Andersohn and his coauthors identified 44,300 who were taking an AED (figure) between January 1990 and September 2005. Of these, 453 were identified who had been diagnosed with suicidal behavior (such as a suicide attempt) or self-harm. In the group, some people were currently taking an AED (defined as using the medication within 14 days of the medical visit). Some people had been on an AED "recently." Recent use was defined as having taken an AED 15–183 days before the medical visit. Past use was defined as having taken an AED 184 days or more before the medical visit.

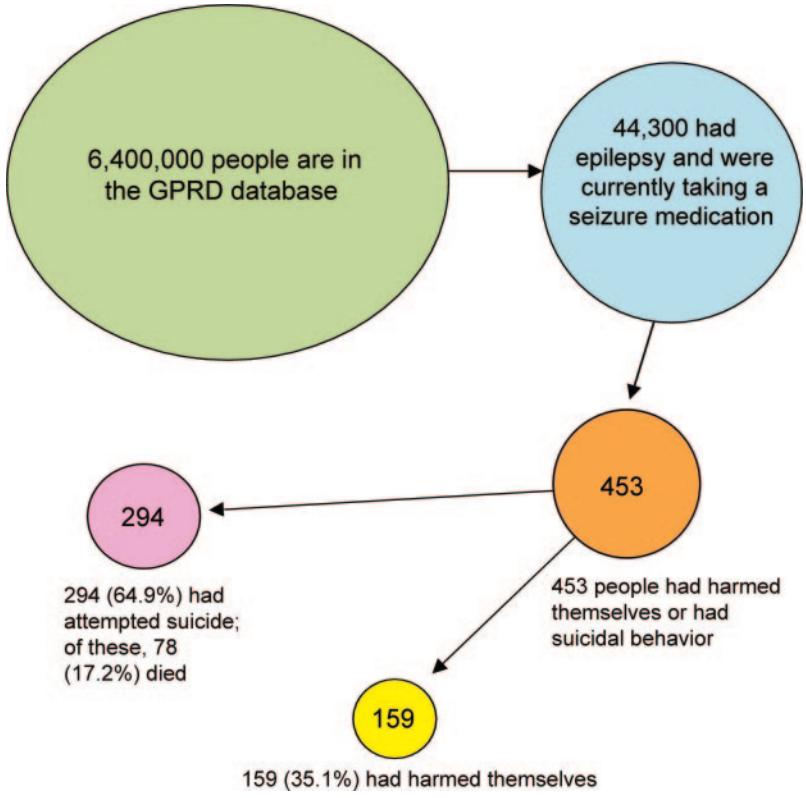
Dr. Andersohn and his coauthors looked at the group very carefully. They divided the group into 4 main categories (table 1). In the first group, they placed people who were taking a barbiturate medication for their seizures. A barbiturate is a sedative—or relaxation—medication. In the second group were people taking conventional AEDs. This would mean that doctors have been using these treatments for a long time. The third group consisted of people taking a newer (more recently developed) AED, one that had a low potential for depression. The authors defined low potential very carefully: in the initial placebo-controlled trials of the AED, there had to be a less than 1% reported incidence of depression. In the last group, people were taking an AED that had been associated with depression more than 1% of the time (in the early trials). This group was labeled as having a high potential for depression.

The results (table 2) showed that group 4, the high potential group, had the most problems. In fact, the results showed that this group was 3 times more likely to have suicidal behavior or self-harm than the control group. The risk of suicidal behavior or self-harm in the other groups was no different from the controls.

In addition, Dr. Andersohn and his colleagues tried to look at individual medications to see if very specific ones caused suicidal behavior or self-harm. Although there were several problems with analyzing the information, levetiracetam seemed to stand out. In other words, people who took levetiracetam seemed to be more likely to commit suicide or hurt themselves than if they were taking another seizure medication.

There were limitations to the study. The General Practice Research Database does not contain information about the severity of the person's epi-

**Figure** The authors carefully looked for patients in the United Kingdom General Practice Research Database (GPRD)




lepsy. Furthermore, it was not possible to analyze a person's specific type of epilepsy. Knowing that certain medicines are used for specific kinds of epilepsy, it may be that the higher rate of suicidal behavior/self-harm was due to the kind of epilepsy, and not the specific medication. Further, because the database included patients to 2005, any medicine approved for use after 2005 would not be included in this analysis.

**WHY IS THIS STUDY IMPORTANT?** It has long been known that seizures, epilepsy, mood problems, and suicide overlap. A study of many AED trials suggests that the medication itself may contribute to this problem. However, the analyses so far have lumped all antiseizure medications together. There might be only a few medications that cause this. Although the study by Dr. Andersohn and his coauthors suggests that levetiracetam is more likely to cause suicidal behavior/self-harm, they also made it clear that we need to study this problem more carefully. Further, it will be important for doctors to look at all available seizure medications, including the ones that were approved for use after 2005.

**Table 1** The authors grouped seizure medications in a specific way

| Groups of antiseizure medication | Generic names of specific medications |
|---|---|
| Barbiturates | Methylphenobarbital, phenobarbital, primidone |
| Conventional | Carbamazepine, ethosuximide, phenytoin, valproate |
| Low risk of depression (<1%) | Gabapentin, lamotrigine, oxcarbazepine, pregabalin |
| High risk of depression (>1%) | Levetiracetam, tiagabine, topiramate, vigabatrin |

**Table 2** The risk of self-harm or suicide in people currently taking an antiseizure medication[a]

| Groups of antiseizure medication | Risk of self-harm or suicide[b] |
|---|---|
| Barbiturates | 0.66 |
| Conventional | 0.74 |
| Low risk of depression (<1%) | 0.87 |
| High risk of depression (>1%) | 3.08 |

[a] Recent or past use of the antiseizure medication did not increase the risk of suicidal behavior or self-harm.
[b] A value of 1.0 means no risk; a value of <1.0 means a reduced risk; a value of >1.0 means an increased risk.

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# About seizures, epilepsy, and mood

**SEIZURES, EPILEPSY, AND MOOD: HOW THEY OVERLAP** Mood disorders and epilepsy overlap quite a bit. This is especially true when a person has seizures that do not stop with antiseizure medications. When seizures are not completely controlled with medicine, they are called refractory. Thirty to fifty percent of people with refractory seizures also have some sort of mood problem. They may have depression, anxiety, or both.

Because epilepsy and mood problems overlap, they are called comorbid conditions. By definition, comorbidity means that the associated illness occurs more often than would be expected compared to populations of patients who do not have the other illness. In other words, if 10% of people have depression, we would expect that 10% of people with epilepsy also would have depression. However, the number is higher (up to 50%). In other words, the overlap cannot be explained by chance. There must be something else that links the two.

However, comorbidity does not imply causality.[2] Even though the two illnesses occur together, this does not mean that one causes the other. What is more likely is that the two illness share a common cause. In other words, the cause of one illness is also the cause of the other. Although not fully understood, an abnormality of neurotransmitters may be the link that connects mood with epilepsy. One thing that is very clear is that the comorbid illness can affect quality of life. In fact, the quality of life of people with epilepsy is influenced more by the presence of depression than the frequency of their seizures.[3]

**MOOD DISORDERS AND EPILEPSY** The link between depression and epilepsy has been observed for centuries: Hippocrates, in 400 BC, said "Melancholics ordinarily become epileptics."[4] In more recent years, this association has been carefully studied. Scientists have tried to better understand how the two illnesses are related. In addition, they have tried to figure out what causes both. In doing this, they hope to be able to develop better therapies or treatments.

The first step in figuring this out was to determine how bad the problem was. In 2005, a survey was sent to over 85,000 people. The survey asked questions about lifelong illnesses like epilepsy, migraine, asthma, and diabetes. The survey also asked questions about mood, specifically bipolar disorder.[5] The goal was to compare the rates of mood problems in people with epilepsy (1,236 respondents), migraine (8,994 respondents), asthma (7,951 respondents), and diabetes (7,342 respondents) vs healthy controls (57,172 respondents). Symptoms of bipolar disorder were found in12.2% of people with epilepsy, 7.2% of people with migraine, 6.3% of people with asthma, 3.2% of people with diabetes, and 1.7% of the controls. In other words, symptoms of bipolar disorder were 6 times higher in persons with epilepsy than in the control group.

Major depressive disorder is defined as having depression for more than 2 weeks. It occurs in about 5.8% of the general population. In those with epilepsy, the number with major depressive disorder is 8%–48% (an average of 29%).[2] In a community-based study on people with epilepsy, the rate of depression was 37%. In patients referred to an epilepsy center, the rate of depression was 50%. Remember that people referred to an epilepsy center usually have refractory epilepsy. In other words, the reason that people in an epilepsy center are more likely to be depressed probably relates to the severity of their epilepsy.[4] What this means is that depression occurs 10 times more often in people with refractory epilepsy than in people who have no medical illness.

The number of people who have epilepsy and anxiety is a little more difficult to figure out. There seems to be a connection between anxiety and seizures.[6] However, this association has been less well-studied than other mood problems. Gabb and Barry[2] stated that the rate of anxiety was 13.3% in the general population. In persons with epilepsy, up to 52% also reported symptoms of anxiety. This may mean that anxiety occurs 4 times more often in people with epilepsy.

**WHEN ILLNESSES OVERLAP, BOTH NEED TO BE TREATED** When people have both epilepsy and depression, studies show that the depression correlates more strongly with a poor quality of life than the frequency of the seizures.[3] A person with epilepsy

needs medication in order to prevent seizures. If he or she also has depression, medication may be needed for this as well.

It has long been known that some medicines that treat seizures also treat mood problems. Carbamazepine, lamotrigine, and valproate are just a few of the seizure medications that also have a positive effect on mood. These medications work in a common way: they increase serotonin levels (serotonin is a neurotransmitter). Higher serotonin levels seem to help to decrease seizures and to improve mood.

In situations where depression (or anxiety) has been identified as a comorbid illness, a neurologist may ask for help from a psychiatrist. With all of the available medications for depression and anxiety, it may be difficult to know which is best for an individual. In addition, the person might need psychotherapy, which is often overseen by a psychiatrist. In other words, a team approach may be needed in order to optimize the person's epilepsy, mood problem, and quality of life.

**CONCLUSIONS** Epilepsy, depression, anxiety, and bipolar disorder commonly coexist. Although there are many possible explanations for why these disorders are comorbid, it is becoming increasingly evident that both epilepsy and mood disorders require treatment in order to achieve the best quality of life. Some antiepileptic drugs are effective for both illnesses: in some instances, selection of one of these agents may result in improvements in both conditions. For other patients, combination therapy may be required. Finally, some people will need psychotherapy in order to have the best results. A team approach that involves a neurologist, psychiatrist, and psychologist may help to get the best treatment for people with epilepsy and mood disorders.

## FOR MORE INFORMATION

AAN.com for patients and caregivers
*http://patients.aan.com/*
Citizens United For Research In Epilepsy (CURE)
*http://www.cureepilepsy.org*
Epilepsy Foundation
*http://www.epilepsyfoundation.org*
Epilepsy Institute
*http://www.epilepsyinstitute.org*
Family Caregiver Alliance/National Center On Caregiving
*http://www.caregiver.org*

## REFERENCES


1. Andersohn F, Schade R, Willich SN, Garbe E. Use of antiepileptic drugs in epilepsy and the risk of self-harm or suicidal behavior. Neurology 2010;75:335–340.
2. Gabb MG, Barry JJ. The link between mood disorders and epilepsy: why is it important to diagnose and treat? Adv Studies Med 2005;5:S572–S578.
3. Gilliam FG, Mendiratta A, Pack AM, Bazil CW. Epilepsy and common comorbidities: improving the outpatient epilepsy encounter. Epileptic Disord 2005;7(suppl 1):27–33.
4. Kanner AM. Depression in epilepsy: a neurobiologic perspective. Epilepsy Curr 2005;5:21–27.
5. Ettinger AB, Reed ML, Goldberg JF, Hirschfeld RM. Prevalence of bipolar symptoms in epilepsy vs other chronic health disorders. Neurology 2005;65:535–540.
6. Beyenberg S, Mitchell AJ, Schmidt D, Elger CE, Reuber M. Anxiety in patients with epilepsy: systematic review and suggestions for clinical management. Epilepsy Behav 2005;7:161–171.

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