SUICIDE AND EPILEPSY

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Suicide, according to WHO, is the tenth leading cause of death world-wide. Studies of suicide in epilepsy are complicated by several factors. Data from 'intractable' epilepsy may not apply to population as a whole. Data from some sources, such as registries and population surveys, or death certificates, may be unreliable. Even in formal prospective studies data have to be corrected for factors such as age and sex. Moreover, the definition of 'suicidality,' which is reported much more frequently than completed suicide, is very imprecise, and may differ from study to study.

Discussion of possible relations of antiepileptic drugs (AEDs) and suicide needs to take into account that the relative risk for suicidal ideation and suicide as a cause of death is two to three times greater among people with epilepsy than the general population. Risk factors include co-morbid psychiatric disease, past attempts, a family history of psychiatric disease or suicide, and an epilepsy diagnosis within six months (Kanner et al 1999).

The US Food and Drug Administration (FDA) conducted a pooled analysis of the relation of suicidality to AEDs using data from 199 placebo-controlled randomized clinical trials of 11 different AEDs including 27,863 active vs 16,029 placebo patients. Trials had to have at least 20 patients in all treatment arms, duration of at least seven days, and trials with no events were excluded. The study population included 25% of patients with epilepsy, 27% with psychiatric disorders, and 48% with pain-related disorders. The overall event number was low. Completed suicide was observed in four patients on AEDs versus none on placebo, attempts thirty versus eight, and ideation 67 versus 29, and total suicidality events 104 to 38. The relative suicidality risk for AEDs versus placebo was 3.5 for epilepsy studies, 1.5 for psychiatric studies, and 1.9 for other studies. Interestingly, the odds ratio for increased sucidality events was much greater in studies performed outside than within North America, a difference that has not been explained. There also were differences in results for individual drugs. Although most had an increased relative risk of sucidality events, only topiramate showed a significant effect. There were no-significant trends for carbamazepine and valproic acid to show decreased suicidality. Phenytoin and Phenobarbital, among other drugs, were no included in the FDA analysis, No clear differences based on presumed AED mechanism of action were found. Based on these data, the FDA issued a warning of increased suicidality risk associated with AED therapy in general.

Several other studies have added additional data. The HealthCore Integrated Research Database Study included 297,620 new episodes of treatment with an anticonvulsant in patients 15 years and older. There were 26 completed suicides, 801 attempted suicides, and 41 violent deaths. The risk of suicidal acts, compared with topiramate, was increased for several drugs, including gabapentin, Lamotrigine, oxcarbazepine , tiagabine, and valproate. Gabapentin users had increased risk in subgroups of younger and older patients, patients with mood disorders, and patients with epilepsy or seizure when compared with carbamazepine (Patorno et al 2010). In contrast, another study in a database of 131,178 patients with epilepsy, pain, bipolar disorder, major depressive disorder and schizophrenia found no overall difference in suicide rates for gabapentin and a significantly reduced rate in psychiatric patients (Gibbons et al 2010).

The United Kingdom General Practice Research Database was used for a nested case-control study 44,300 patients with epilepsy on AEDs. Patients with self-harm or suicidal behavior were identified by predefined codes. 453 cases were compared with 8,962 age-matched and sex-matched controls. AEDs were classified into four groups: barbiturates, conventional AEDs, newer AEDs with low (lamotrigine, gabapentin, pregabalin, oxcarbazepine) or high (levetiracetam, tiagabine, topiramate, vigabatrin) potential of causing depression. Current use of newer AEDs with high potential of causing depression were associated with a significant 3-fold increased risk of self-harm/suicidal behavior; but the difference was only evident in patients with psychiatric co-morbidity (Anderson et al 2010).

A study based on the Danish National Prescription Registry included 169,725 AED prescriptions, only 2.6% of which were for epilepsy. Overall, AEDs increased the risk of completed suicide (OR 1.85 (95% C.I. 1.4-2.5), with significant effects for clonazepam, valproic acid, Phenobarbital, and lamotrigine (Olesen et al 2010).

The United Kingdom Health Improvement Network study, with 6.7 million patients in its database, included patients if enrolled in a clinical practice for at least 6 months from 7/1/1988-3/31/2008, and an episode of suicide, attempted suicide. Patients with a family history of suicide or a prior attempt were excluded. Five controls were selected randomly for each case. Adjusted for co-variates, current AED used increased the risk of suicide only in patients with epilepsy and either depression or bipolar disorder (Arana et al 2010).

Some of the differences among the studies are due to the structure of the underlying databases, varying diagnoses among the patients, and in the AEDs for which data are available. Other confounders could include retrospective designs, treatment indications, and effects of population factors, co-morbidities, and drug interactions. However, it is interesting to consider that a pattern of increased risk for sucidality is

associated in patients with depression or other psychiatric disorders in several studies. This factor could underlie the results of the FDA analysis. At this point, it is not clear how much AEDs increase the risk of suicide, but enough data are available to suggest that it is probably real, at least in some subgroups of patients with epilepsy. Several factors are important to consider in assessing the potential risk for increased sucidality in AED treatment of patients with epilepsy. The overall risk of depression and suicide increased in epilepsy, and patients should always be asked about their, mood, past personal and family history of depression, past suicide attempts, and current ideation. Depression in epilepsy must be recognized and treated. Some AEDs appear to increase risk, and drugs associated with an increased risk for depression in epilepsy, particularly barbiturates, should be used carefully. Potential suicide risk factors should be considered in matching AED choice to each patient.

References:

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