DO AEDS CONTRIBUTE TO SUICIDE RISK IN EPILEPSY? YES

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In 2008, the Food and Drug Administration (FDA) issued an alert to health care professionals about an increased risk of suicide ideation and behavior in people treated with antiepileptic drugs (AEDs) (FDA 2008a,b). Since then, a number of retrospective cohort and case-control studies have been published trying to address this issue but gathered results are contradictory. This condensed manuscript focusses on data suggesting that AEDs increase the suicide risk in people with epilepsy. The interested reader is referred to the more comprehensive literature review in the recent ILAE (International League Against Epilepsy) consensus paper on this topic by Mula et al., 2013.

The FDA alert to health care professionals about an increased risk of suicide ideation and behavior in people treated with AED came from a meta-analysis of multicenter-randomized placebo controlled trials of 11 AEDs. Pharmaceutical companies had been previously asked to submit data from these trials, regardless of indication, with at least 30 patients involved. Spontaneously reported suicidality occurring during double-blind trials with an AED were sought and categorized. Data were provided on the use of carbamazepine, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, valproate, and zonisamide used for epilepsy (25% patients), psychiatric indications (27% patients) and 'other conditions' (48% patients). In the main analysis, almost 28,000 people taking AED and over 16,000 people taking placebo were considered. There were four completed suicides altogether, all in people taking AEDs and none in those taking placebo. The FDA concluded that patients receiving AEDs were significantly more likely to experience suicidal behavior or ideation compared with placebo (OR 1.8; 95% CI 1.24 - 2.66). In addition, they observed that the relative risk (RR) vs. placebo was higher in patients treated for epilepsy (RR = 3.6; 95% CI 1.3-12.1) than for selected psychiatric illnesses (RR = 1.6; 95% CI 1-2.4) or other conditions (e.g., migraine and neuropathic pain; RR = 2.0; 95% CI 0.8-4.8) (FDA 2008b) where RR were not significant. As a result of the analysis, the FDA required that all manufacturers of drugs in this class include a warning in their labeling and develop a medication guide for patients, informing them of the risks of suicidal thoughts or actions (Busco 2008).
The FDA data was received with great skepticism by clinicians and professional societies, including the American Epilepsy Society, and some investigators questioned the validity of its findings, after identifying serious methodological flaws and suggested that the FDA's concern might have been excessive (Hesdorffer and Kanner 2009, Mula, et al. 2010), and that the risk of stopping (or not even starting) AEDs in people with epilepsy would be far greater than this hypothetic small increased risk of suicidality (Mula and Sander 2010).

The FDA's warning indicates an increased risk of suicide with all AEDs, despite the fact that statistical significance was found in only 2 (i.e., topiramate and lamotrigine) of the 11 AEDs studied. Furthermore, inclusion of three additional studies of lamotrigine resulted in the loss of statistical significance for this AED. Two other AEDs, valproic acid and carbamazepine, actually yielded a "small protective effect".
Since 2010 a number of retrospective cohort and case-control studies, using observational study methodology, investigated whether or not there is an association between AEDs and suicidality, three of which confirmed an increased risk related to AED (Andersohn et al. 2010, Patorno et al. 2010, VanCott et al. 2010). However, there are several methodological issues which need to be considered, in particular adjustment for prior suicidal behavior (Mula and Hesdorffer 2011).
In patients with epilepsy, the overall risk of committing suicide is about three times higher than that of the general population (Bell, et al. 2009, Christensen, et al. 2007, Harris and Barraclough 1997). Several studies have attempted to identify reasons for such an increased risk. In fact, suicidality and epilepsy have a complex relation, based on several variables.
In the general population, about 90% of people who successfully commit suicide have at least one psychiatric disorder at that time (Barraclough 1987). A Danish study pointed out that the rate ratio of suicide in people with epilepsy is still doubled even after excluding people with psychiatric comorbidity and adjusting for various factors and increases by 32-fold in the presence of comorbid mood disorders and by 12-fold in the presence of anxiety disorders and schizophrenia. Post-ictal suicidal ideation is relatively frequent in patients with treatment-resistant partial epilepsy, having been identified in 13% of 100 consecutive patients with a median duration of 24 hours (Kanner, et al. 2004). Furthermore, a bidirectional relation has been identified between suicidality and epilepsy, whereby patients with a

history of suicidal behavior have a five-fold higher risk of developing epilepsy in a population-based study conducted in Iceland (Hesdorffer, et al. 2006). This bidirectional relation raises the question of common pathogenic mechanisms operant in both conditions such as serotonin dysfunction, a hyperactive hypothalamic pituitary-adrenal axis as well as glutamate and GABA-ergic disturbances (Hecimovic, et al. 2011).
The psychotropic potential of AEDs in patients with epilepsy is related to direct and indirect mechanisms (Mula and Sander 2007). A number of studies suggest that treatment with some AEDs is associated with the occurrence of symptoms of depression while other compounds have positive psychotropic properties. As far as first generation compounds are concerned, authors agree that there is a link between barbiturates and depression, while carbamazepine probably has mood stabilizing and anti-manic effects (Dodrill and Troupin 1977, Robertson and Trimble 1983, Rodin, et al. 1976). Among second generation AEDs, vigabatrin (Levinson and Devinsky 1999), tiagabine (Trimble, et al. 2000) and topiramate (Mula, et al. 2003a) have been linked to treatment-emergent depressive symptoms while levetiracetam with dysphoria and mood lability (Mula, et al. 2003b).
In some cases, treatment-emergent depressive symptoms are associated with a sudden complete control of seizures (the forced normalization phenomenon) (Ring, et al. 1993), while in others they are unrelated to this. Several studies pointed out that the development of psychiatric adverse events (which could potentially facilitate the occurrence of suicidal ideation and behavior) is more likely in patients at risk of developing psychiatric disorders, either because of a past psychiatric history or a family psychiatric history (Kanner, et al. 2003, Mula et al, 2007).

CONCLUSIONS

AEDs can be associated with treatment-emergent psychiatric problems that can lead to suicidal ideation and behavior. The psychiatric and suicide risks differ between the different types of AED suggesting specific psychotropic profiles. The actual suicidal risk is yet to be established, but seems to be very low.

Suicidality in epilepsy is multi-factorial. Major operant variables include: (i) post-ictal suicidal ideation; (ii) sudden seizure freedom as in forced normalization and the psychological phenomenon of “burden of normality” (iii) a past and/or current history of psychiatric disorders, particularly mood and anxiety disorders (and above all when associated with prior suicidal attempts); (iiii) a family history of mood disorder complicated with suicidal attempts. Given the above risks, clinicians should investigate the existence of such risk factors (including suicidality before the onset of epilepsy) and if necessary, refer the patient for a psychiatric evaluation, but not withhold treatment even in patients with positive suicidal risks. The risk of stopping AEDs or refusing to start AEDs is significantly worse and can actually result in serious harm including death to the patient (Hesdorffer, et al. 2011, Ryvlin, et al. 2011).

When starting an AED or switching from one to other AEDs, patients should be advised to report any changes in mood and suicidal ideation to their treating physician. In fact, despite the uncertainty, the FDA alert remains active and clinicians need to screen patients they start on AEDs.
The Columbia Suicide Severity Rating Scale (C-SSRS) represents a suitable and reliable instrument to evaluate suicidality (Posner, et al. 2011) and it is available in several languages).

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