

In 2008, the Food and Drug Administration (FDA) issued an alert about an increased risk of suicide ideation and behavior in people with epilepsy treated with antiepileptic drugs (AEDs) [1] and this was based on a meta-analysis of spontaneously reported suicidal ideation and behaviors from multicenter, randomized, placebo-controlled studies of 11 AEDs [2]. An *ad hoc* Task Force of the International League Against Epilepsy (ILAE) discussed the limitations of the FDA meta-analysis, especially the assessment of suicidality in trials not designed to prospectively assess suicidality [3]. Subsequently, a number of authors have tried to confirm or confute the FDA's findings but most of these studies were also affected by a number of methodological limitations [4].

There is no doubt that AEDs have a psychotropic potential, as they modify neuronal pathways that are not only relevant for seizure control, but also for mood and behavior [5]. **In fact, some AEDs are successfully used in the treatment of mood and anxiety disorders [5-6].** However, AEDs may also have negative psychotropic properties and this seems to be more evident in epilepsy as compared to other neurological conditions where AEDs are frequently prescribed such as neuropathic pain, migraine or movement disorders, and this probably because epilepsy *per se* is associated with an increased prevalence of behavioral abnormalities [6]. For all these reasons, the issue of suicide during treatment with AEDs in patients with epilepsy is more complex than just a treatment-emergent adverse event.

In the past, the FDA issued other alerts about drug-induced suicidality and everybody is aware of the quite controversial black-box warning about antidepressants, SSRIs in particular, issued in 2004. Consequences of that warning have been discussed by a number of authors [7-8] and, in 2007, the FDA has expanded that warning stating that depression itself is associated with an increased risk of suicide. However, this hasn't happened for epilepsy yet, despite the increasing amount of evidence showing that epilepsy is associated with an increased risk of suicide.

In the general population, suicide accounts for 1.5% of all deaths, representing the 10<sup>th</sup> cause of death, with an incidence of 10.7/100,000 per year [103]. However, the standard mortality ratio for suicide in patients with epilepsy is three times higher than that of the general population [9]. In fact, suicide accounts for 11.5% of all deaths in epilepsy [10], with incidence rates of 16.9/100,000 per year [11]. Several authors have attempted to identify reasons for such an increased risk. Severity of the seizure disorder does not seem to play a role [12] and even if depression seems to be one of the most important predictors, suicide risk remains high even after excluding patients with a history of psychiatric disorders and adjusting for socioeconomic factors, suggesting that epilepsy *per se* is associated with an increased risk of suicide [13]. Some authors have suggested a link particularly with temporal lobe epilepsy [14] but this is not supported by other studies [15]. It is, therefore, evident that other, still unidentified, factors contribute to the increased risk of suicide in epilepsy.

Someone may argue that the increased risk of suicide observed in epilepsy is given by the AED treatment and, for this reason, patients with epilepsy present with a higher risk as compared to the general population. However, epidemiological data about the bidirectional relationship between epilepsy and suicide clearly show that this is not the case and suggest

the presence of other factors, probably biological and intrinsic to the pathophysiology of epilepsy [16]. In addition to that, there is no doubt that psychosocial factors play also an important role [17]. According to the interpersonal theory of suicide, the simultaneous presence of thwarted belongingness (i.e. not feeling accepted by others) and perceived burdensomeness (i.e. the belief that one is a burden on others or society) produce the desire of suicide [18] and, unfortunately, it is highly possible that these two phenomena co-occur in people with epilepsy as this is still a highly stigmatized condition in both high- and low-income countries [17].

For a long time, suicide has been considered an unmentionable issue in epilepsy [19] but the FDA alert has finally forced the scientific community to face the problem. **Since 2008, the number of publications about suicide in epilepsy has increased exponentially with 14 publications on PubMed in 2008, 24 in 2009 and 46 in 2010.** Drug companies now collect routinely data about suicide during regulatory trials of AEDs. Clinicians are now becoming aware of the problem but a lot of work still needs to be done as the majority of patients are still inadequately counseled about mood disorders in epilepsy and the majority of epileptologists are still reluctant to screen their patients for depression and even more for suicide. Several clinical instruments have been validated in people with epilepsy for the periodic screening of depression and the Neurological Depression Disorder Inventory for Epilepsy (NDDIE) has also been validated for suicide screening [20]. **The major barrier to prevention of suicide in epilepsy is the lack of training in psychiatry for the majority of neurologists making them uneasy with this kind of conversation. The routine use of the NDDIE in the outpatient setting would facilitate clinicians in discussing about these problems with their patients and would stimulate the development of shared clinical pathways between epilepsy centers and local psychiatric services.**

In May 2013, the World Health Organization (WHO) issued the first-ever Mental Health Action Plan of which suicide prevention is an integral part, with the goal of reducing suicide rates worldwide by 10% by 2020 [21]. This is an excellent opportunity for the epilepsy community to gain awareness about suicide in epilepsy and for neurologists to develop appropriate prevention strategies in conjunction with local psychiatric services, as prevention is the only treatment for suicide. Over time, the management of epilepsy has become more and more complex requiring inputs from different health professionals. Epilepsy centers should offer access to different services depending on individual needs of patients, including specific pathways for access to mental health and prevention strategies for suicide according to local facilities available. In this context, an endorsement from FDA that epilepsy is associated with an increased risk of suicide, as it happened for depression, would probably stimulate physicians, at different care levels (from primary care to secondary and tertiary care services), to implement prevention strategies and include routine screening for depression in their care pathways.

After almost 10 years, evidence favoring or contrary to the FDA alert is still lacking. Suicide is a complex phenomenon requiring careful attention and understanding and for this reason further research in epilepsy is urgently needed while ignoring, or even worse **minimizing** the problem, is totally unacceptable.

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