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Antiepileptic drugs and the risk of suicide in patients with epilepsy

Leki przeciwpadaczkowe a ryzyko samobójstwa u chorych na padaczkę

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Abstract

It is estimated that the risk of suicide in epileptic patients is about three times higher than in the general population. Suicide risk factors in this group of patients include age, gender, socio-economic factors, history of psychiatric disorders and epilepsy itself. According to a warning issued by the Food and Drug Administration in 2008, which was based on a meta-analysis of randomised controlled trials of 11 compounds, antiepileptic drugs are one of them. This warning was criticised by many investigators and the International League Against Epilepsy task force because of methodological limitations. Although some of the antiepileptic drugs may have negative influence on mood, contributing to suicidal ideation, the actual risk of suicide seems to be low. It should be taken into account that the discontinuation of antiepileptic therapy may increase the risk of suicide to a greater extent than taking antiepileptic drug alone. A recent meta-analysis did not confirm the increased risk of suicide in patients treated with antiepileptics. Almost 15 years after the Food and Drug Administration issued the alert about an increased suicidality risk with antiseizure medications, there is still considerable debate on this subject. The available literature data has shown no obvious causal relationship between antiseizure medications and the risk of suicide. The authors of the studies point to the complex relationship between suicide and epilepsy, highlighting the bidirectional relationship and the influence of many factors.

Keywords: epilepsy, anticonvulsants, suicide

Streszczenie

Szacuje się, że ryzyko samobójstwa w grupie chorych z padaczką jest około trzech razy większe niż w populacji ogólnej. Do czynników ryzyka samobójstwa w padaczce zalicza się: wiek, płeć, czynniki społeczno-ekonomiczne, schorzenia psychiatryczne w wywiadzie i czynniki związane z samą padaczką. Zgodnie z ostrzeżeniem wydanym w 2008 roku przez Agencję ds. Żywności i Leków ryzyko wzmagają także leki przeciwpadaczkowe. Ostrzeżenie to, oparte na metaanalizie randomizowanych kontrolowanych badań 11 cząsteczek, ze względu na ograniczenia metodologiczne było krytykowane przez licznych badaczy i grupę zadaniową przy Międzynarodowej Lidze Przeciwpadaczkowej. Chociaż niektóre leki przeciwpadaczkowe mogą mieć negatywny wpływ na nastrój, co prowadzi potencjalnie do myśli samobójczych, rzeczywiste ryzyko samobójstwa wydaje się niewielkie. Należy brać pod uwagę, że przerwanie terapii lekami przeciwpadaczkowymi może zwiększyć ryzyko samobójstwa w znaczniejszym stopniu niż ich przyjmowanie. Wyniki niedawno opublikowanej metaanalizy nie potwierdziły podwyższonego ryzyka samobójstwa u chorych leczonych lekami przeciwpadaczkowymi. Prawie 15 lat po wydaniu przez Agencję ds. Żywności i Leków ostrzeżenia o zwiększonym ryzyku samobójstwa związanym ze stosowaniem leków przeciwpadaczkowych wciąż toczy się poważna debata na ten temat. Dostępne dane z literatury nie potwierdzają oczywistego związku przyczynowego między lekami przeciwpadaczkowymi a ryzykiem samobójczym. Autorzy badań podkreślają złożoność związku między samobójstwem a padaczką, zwracając uwagę na dwukierunkowe zależności i wpływ licznych czynników.

Słowa kluczowe: padaczka, leki przeciwpadaczkowe, samobójstwo

EPIDEMIOLOGY OF SUICIDES

According to World Health Organization (WHO) estimates, more than 700,000 people commit suicide each year, i.e. someone takes their own life every 40 seconds (WHO, 2023), with 78% of cases occurring in low- and moderate-income countries. Suicide is the second leading cause of premature death in the 15–30 age group, following traffic accidents (Bertolote and Fleischmann, 2002). It is estimated that the risk of suicide is about three times higher in epileptic patients than in the general population (Bell et al., 2009a; Christensen et al., 2007).

SUICIDE RISK FACTORS IN PATIENTS WITH EPILEPSY

Suicide risk factors in epileptic patients include age, gender, socioeconomic factors, a history of psychiatric disorders and factors related to epilepsy itself (Giambarberi and Munger Clary, 2022). Suicide risk tends to decrease with age and is highest among adolescents with epilepsy (Christensen et al., 2007; Nigussie et al., 2021). In the population analysed in the present study, suicidal ideations were more common in women, even independently of depression (Kim et al., 2020; Nigussie et al., 2021), while more suicide attempts and suicides were observed among men (Abraham et al., 2019). Factors such as being single, divorced, widowed or having poor social support significantly increase the risk of suicidal ideations (Nigussie et al., 2021). Patients with epilepsy are more likely than the general population to suffer from comorbid psychiatric disorders, which also significantly increase the risk of suicidal behaviour (Christensen et al., 2007; Erlangsen et al., 2020; Hesdorffer et al., 2016; Josephson and Jetté, 2017). Suicidal ideations are more common in patients with a positive family history of suicide, regardless of depression (Kim et al., 2020; Nigussie et al., 2021). The impact of epilepsy-related factors is unclear. According to some researchers, the risk of suicide increases soon after the diagnosis of epilepsy and is elevated in patients with at least one epileptic seizure per month (Christensen et al., 2007; Kim et al., 2020). This raises the following question: do antiseizure medications (ASMs) alone increase the risk of suicide?

FDA WARNING LETTER

In 2008, the U.S. Food and Drug Administration (FDA) issued a warning regarding the increased risk for suicidality in patients on ASMs. This warning was based on a meta-analysis of 199 randomised placebo-controlled clinical trials including 11 ASMs (felbamate, gabapentin, carbamazepine, valproate, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate and zonisamide). Among 43,892 patients (27,863 on ASMs and 16 029 – placebo) treated for epilepsy (31% of trials), psychiatric disorders (28%), and other conditions (41%), mainly pain, the risk of suicide was increased 1.8 fold with ASMs compared to placebo (Food and Drug Administration, 2008). In accordance with the FDA's decision, a warning about the risk for suicidality was added to ASMs' leaflets (Food and Drug Administration, 2008).

METHODOLOGICAL LIMITATIONS OF THE FDA WARNING

It was only one year after the FDA warning was issued that methodological limitations were pointed out. First of all, the study group was heterogeneous and data were collected retrospectively. Second, all ASMs were grouped together although their risks varied, including statistically nonsignificant increase for 7 of 11 and decrease for 2 of 11 medications. Third, drug indications varied (only 31% of the studies concerned epilepsy). Fourth, both monotherapy and adjunctive therapies were analysed. Fifth, baseline suicidality risk was not accounted for (Hesdorffer and Kanner, 2009). The latter aspect is important because a population-based study in Denmark showed that the risk of suicide for those making a second attempt was found to be significantly higher than for those making a first attempt (Christiansen and Jensen, 2007). During a follow-up period of 5 years, 30% of people made a second attempt, while only 0.32% made a first attempt. Similar results were obtained for completed suicides (2.33% vs. 0.04%) (Christiansen and Jensen, 2007).

THE POSITION OF ILAE ON FDA WARNING

In 2013, a Task Force established by the International League Against Epilepsy (ILAE) published a position paper on the FDA warning (Mula et al., 2013). Among other things, the paper highlighted that the suicide risk assessment was based on "spontaneous" patient reports instead of questionnaires routinely completed by all subjects. The FDA's warning indicates an increased risk of suicide with all ASMs, despite the fact that statistical significance was found in only 2 (i.e., topiramate and lamotrigine) of the 11 ASMs evaluated. The position paper also noted that suicide risk is higher in some geographic regions, so the data cannot be generalised. In addition, the ILAE highlighted that most epilepsy trials (92%) assessed by FDA included patients on adjunctive therapy, including psychiatric drugs (Mula et al., 2013). The risk of suicide during ASM therapy depended on the indication under which the drugs were used. In a British population-based study, ASMs did not increase the risk of suicide-related events in epilepsy (without comorbid depression or bipolar disorder), but only in depression alone and in people treated with ASMs for other indications (Arana et al., 2010).

NEGATIVE CONSEQUENCES OF FDA WARNING

Researchers point out that the FDA's warning could have negative consequences. The analysis conducted by the FDA

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indicated a significantly (1.95 times) increased risk of suicide in patients taking selective serotonin reuptake inhibitors (SSRIs) (Hammad et al., 2006), while systematically collected data did not suggest a link between suicidal behaviour and SSRI use (Mann et al., 2006). Although fewer antidepressants were prescribed to children and adolescents after the warning was published, suicide rates increased in the analysed age group (Gibbons et al., 2007; Nemeroff et al., 2007).

THE RISK OF SUICIDE AFTER THERAPY DISCONTINUATION

It is noteworthy that the risk of suicide associated with discontinuing or not starting therapy may be higher than that associated with the use of ASMs (Bell et al., 2009b; Hesdorffer and Kanner, 2009). The suicide rate in epileptic patients is higher than in the general population, but the number of suicide deaths appears to be significantly lower than the number of deaths due to accidents and sudden unexpected death in epilepsy (SUDEP), which are associated with uncontrolled seizures (Bell et al., 2009a; Christensen et al., 2007; Forsgren et al., 2005; Surges et al., 2009). It has been confirmed that noncompliance with ASMs can have serious or fatal consequences for epileptic patients and is associated with a threefold increase in the risk of death compared to compliant patients (Faught et al., 2008).

THE EFFECTS OF ANTIEPILEPTIC DRUGS ON MOOD AND BEHAVIOUR

ASMs are still the mainstay of treatment for epilepsy, but in addition to reducing the number of epileptic seizures, they can affect the patient's mood and behaviour. Some (but not all) ASMs can induce psychiatric adverse effects and lead to suicidal ideations. The degree of suicidal risk has yet to be determined, but nevertheless appears to be very low (Mula et al., 2013). Depression is often a consequence of stimulation of the GABAergic system. According to ILAE and FDA recommendations, doctors should instruct their patients to report mood changes and the occurrence of suicidal ideations at the stage of including or switching ASMs (Mula et al., 2013, 2003).

SUICIDE RISK ASSESSMENT

Tools to assess for suicide risk are available. One of these is the Columbia Suicide Severity Rating Scale (C-SSRS), developed by researchers at Columbia University, the University of Pennsylvania and the University of Pittsburgh (Oquendo et al., 2003). The utility of the tool for assessing suicidal ideations and behaviours in clinical and research settings has been confirmed in studies (Posner et al., 2011). C-SSRS allows for a comprehensive assessment of suicidal behaviours and ideations, as well as comparing findings across clinical populations. Following FDA recommendations, suicide risk must be assessed prospectively in clinical trials since 2008, for which C-SSRS has been used since 2011.

THE RISK OF SUICIDE IN PATIENTS RECEIVING ASMs – THE LATEST DATA

A 2021 meta-analysis of 17 randomised controlled trials prospectively assessed suicidality in patients treated with five ASMs: eslicarbazepine, perampanel, brivaracetam, cannabidiol and cenobamate (Klein et al., 2021). The studies included a total of 5,996 patients, of whom 4,000 patients were treated with ASMs. C-SSRS was used in seven studies. No increased risk of suicide for the evaluated ASMs was confirmed.

CONCLUSIONS

Nearly 15 years after the FDA issued a warning on the increased suicidality associated with the use of ASMs, there is still considerable debate on the subject. The generally available literature data does not support the causal relationship between ASMs and suicidal risk. On the contrary, authors emphasise the complex correlation between suicide and epilepsy, bidirectional relationships and the contribution of multiple factors.

Conflict of interest

The author reports no financial or personal relationships with other individuals or organisations that could adversely affect the content of the publication and claim ownership of this publication.

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