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Marco Mula

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REVIEW

Suicidality and antiepileptic drugs in people with epilepsy: an update

Marco Mula

Institute of Medical and Biomedical Education, St George's University of London and the Atkinson Morley Regional Neuroscience Centre, St George's University Hospitals NHS Foundation Trust, London, UK

ABSTRACT

Introduction: Almost 15 years after the Food and Drug Administration (FDA) issued an alert about an increased suicidality risk with antiseizure medications (ASMs), there is still considerable debate on this subject.

Areas covered: This is a review of the role of ASMs in the context of suicide in epilepsy.

Expert opinion: After an explosion of research shortly after the FDA warning was released, only a limited number of studies were published in more recent years, and they did not overcome the limitations of previous studies. Overall, available literature does not support an obvious causal relationship between ASMs and suicide. On the contrary, studies are highlighting the complex relationship between suicide and epilepsy, strengthening the bidirectional relationship and the multifactorial origin.

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Epilepsy; suicide; depression; antiepileptic drugs; antiseizure medications

1. Introduction

Antiseizure medications (ASMs) still represent the main treatment for epilepsy, but they can have an impact on mood and behavior in addition to their effects on seizures.

In 2008, the Food and Drug Administration (FDA) issued an alert about an increased suicidality risk with ASMs in people with epilepsy, grounded on a meta-analysis of randomized controlled trials of 11 compounds [1]. Data were based on spontaneous reporting during double-blind trials of ASMs for any indication (25% people with epilepsy) and involved carbamazepine, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, valproate, and zonisamide. There were four completed suicides among patients taking these ASMs and none in the placebo group and the FDA concluded that patients on ASMs had an increased suicidality risk as compared to those on placebo (OR 1.8 95% CI 1.2 2.7) with a Relative Risk (RR) of 3.6 (95% CI 1.3–12.1) for people with epilepsy, while it was only slightly increased for patients with psychiatric disorders (RR 1.6 95% CI 1–2.4) and non-significant for other conditions, mainly pain (RR 2 95% CI 0.8–4.8).

In 2013, an *ad hoc* Task Force of the International League Against Epilepsy (ILAE) published an Expert Consensus Statement pointing out the limitations of the FDA meta-analyses and the complexities behind suicide in epilepsy to limit this phenomenon to a side effect of ASMs but emphasized the need for suicide screening in clinical practice and monitoring during clinical trials [2]. Nonetheless, as a consequence of the FDA alert, the increased suicidality risk is now present on the information leaflets of almost all ASMs.

In the subsequent years, a number of authors have attempted to provide new data in order to clarify this issue. This is a narrative review of the available data on ASMs and suicidality in people with epilepsy. Articles published up to 1 April 2022 were identified through PubMed using the search terms 'antiepileptic drugs,' 'suicide,' 'epilepsy.' No language restrictions were applied.

2. Studies on antiseizure medications and suicide in epilepsy

The search generated 272 abstracts. A total of 11 studies (four case-control and seven cohort studies) and one meta-analysis have been included in this review (Table 1). Four studies clearly show no increased suicide risk with ASMs [3–6]. A meta-analysis of Phase 2 and Phase 3 studies of eslicarbazepine, perampanel, brivaracetam, cannabidiol, and cenobamate involving more than 5,000 patients shows no increased suicidality risk for these specific ASMs [7]. One study shows increased risk for clobazam, valproate, lamotrigine, phenobarbital, and levetiracetam as compared to carbamazepine [8]. One study shows increased risk for levetiracetam and lamotrigine as compared to gabapentin [9]. One study shows increased risk for gabapentin, lamotrigine, oxcarbazepine, tiagabine, and valproate as compared to topiramate [10].

Of the 11 studies, only one focuses specifically on patients with epilepsy [11]. In three studies, people with epilepsy represent a subsample of the population investigated. Four studies focus on elderly patients (age older than 65) as data come from the Veterans Health Administration inpatient and outpatient care database.

In terms of regional representation, in six studies, data come from U.S. population, three studies use data coming from the UK, and two studies use data from the Danish population.

CONTACT Marco Mula mmula@sgul.ac.uk Epilepsy Group Atkinson Morley Regional Neuroscience Centre, St George's University Hospital NHS Foundation Trust, Blackshaw Road, London SW17 0QT, UK

Article highlights

- One in four people with epilepsy present a lifetime history of suicidal thoughts; one in eight during the last 12 months; 4% suicide attempts in the last 12 months
- Suicide in epilepsy is multifactorial and due to biological, psychological, and social factors
- One in six people with epilepsy develop psychiatric side effects of ASMs and 0.17% suicidal ideation
- There are no robust head-to-head comparison trials providing strong evidence for that supposed safety of some ASMs
- Periodic screening, identification of comorbidities, and close clinical monitoring represent the most appropriate strategy
- Trailing any ASM in a safe environment is much more beneficial for patients than just choosing a low-risk ASM in an unsafe environment

All studies adjust for socio-demographic variables and medical factors such as number and type of medical comorbidities. However, only four studies consider the previous history of suicide as a confounding factor, while a large majority (7 out of 11) considers previous history of psychiatric disorders as a potential confounding factor.

In terms of ASMs, three studies investigate the relative risk as compared to an index drug, namely carbamazepine [8], gabapentin [9], and topiramate [10], while the majority of studies compare subjects generally exposed to the ASMs against those not exposed. As already stated, all studies present data on patients exposed to ASMs independent on diagnosis and only three studies report data coming from people with epilepsy specifically as a subgroup [3,9,12].

In terms of outcome, all studies investigate suicidality (ideation, behavior, and attempt), as well as complete suicide apart from one study, which focuses on psychiatric symptoms in general, including suicide [6]. One case control cohort study in veterans older than 65 elaborates also a propensity score for suicide events [13]. One case-control study looks at the problem from a slightly different angle comparing those who committed suicide against controls and investigates current use of ASMs against previous use of ASMs [14]. The authors identify a slightly increased risk for current users and such risk was increased specifically for phenobarbital (OR 1.26 95% CI 1.13–1.40) [14].

3. Discussion

In general terms, all studies identified in Table 1 have largely failed to identify an obvious causal relationship between ASMs and suicide in epilepsy. However, it has to be pointed out that almost all studies suffer from a number of methodological limitations, and we are still far from the ideal study providing conclusive data on this subject.

Lack of control for previous suicidal behavior and the lack of a standardized psychiatric assessment are the major limitations. Even in DSM-5, it is emphasized that individuals remain at higher risk for suicide attempts and death in the 24 months after a suicidal attempt. For all these reasons, a previous history of suicidal behaviors in, at least, the previous 24 months represents a major confounding factor. Still, data come from three main geographical areas only and suicide has important regional variations. Finally, the results of the meta-analysis of regulatory trials [7] are relatively relevant in this context as it is well known that people with previous suicidal ideation or even a past history of psychiatric disorders are almost always excluded from clinical trials. The National Institute of Neurological Disorders and Stroke (NINDS) clearly states that subjects with active suicidal plan/intent in the past 6 months, a history of suicide attempt in the last 2 years or more than 1 lifetime suicide attempt should be excluded from clinical trials of ASMs [15]. Therefore, the findings of the meta-analysis apply to a selected low-risk population group and cannot be transferred to the general population of people with epilepsy seen in routine clinical practice that is the main subject of the FDA alert. But if studies published so far do not seem to provide strong evidence for a causal relationship between ASMs and suicide, there is no doubt that suicide represents a relevant clinical problem in people with epilepsy. It is, therefore, important to understand the potential role of ASMs in this context and where the association identified by the FDA meta-analysis comes from. What is the place of ASMs among different potential contributors to suicide in epilepsy? Can ASMs be a precipitating factor in predisposed individuals? To address all these questions, a few points need to be analyzed.

3.1. The relationship between epilepsy and suicide

It is now established that suicide in epilepsy is more frequent than the general population and people with epilepsy represent a high-risk population. In fact, suicide represents 11.5% of all causes of death in epilepsy against 1% of the general population [16]. That suicide was frequent in epilepsy was already known more than 40 years ago. A two-year study of patients admitted to hospital after a deliberate self-harm published in 1980, already shows a fivefold excess of patients with epilepsy as compared with general population prevalence rates. Male patients with epilepsy are particularly overrepresented, and the study points out that patients with epilepsy are prone to make repeated attempts, thus pointing out the importance of previous suicide behavior as a risk factor [17].

In more recent times, epidemiological studies have shown that one in four people with epilepsy present a lifetime history of suicidal thoughts and one in eight during the last 12 months, with a 4% prevalence of suicide attempts in the last 12 months [18]. In 2017, The Mortality Task Force of the International League Against Epilepsy (ILAE) has finally acknowledged suicide as one of the causes of increased mortality in people with epilepsy with a 3 to 5 times increased risk as compared to the general population [19].

Despite clear evidence of such an increased risk, the reasons for that are still unclear and are likely to be multifactorial. In fact, potential reasons consist of biological, psychological, and social factors. Psychiatric disorders are generally more frequent in people with epilepsy than in the general population, representing the background increased risk for suicide [20]. Epilepsy is even today a highly stigmatized condition and those with mental health problems are burdened by what is known as ‘double-stigma’ leading to a vicious cycle that increases social isolation and contributes to underutilization

Table 1. Summary of studies investigating suicide with antiseizure medications.

	Study design	n	Epilepsy	Comparison drug	Outcome measure	Results	Control for prior suicidal behavior	Control for prior mood disorder	Standardized psychiatric assessment	Adjustment for confounders
Olesen et al. 2010 [8]	Case-crossover/Cohort analysis	6,780	-	CBZ/No ASM	Suicide events	Increased risk for CLB, VPA, LTG, PB, LEV	-	+	-	Demographic and medical factors
VanCott et al. 2010 [9]	Case-control (>66) new prescription	112,096 (epilepsy 7,445)	±(subgroup)	GBP	Suicide behaviors	Increased risk for LEV, LTG	+	+	-	Demographic and medical factors
Patorno et al. 2010 [10]	Cohort (new AEDs users)	297,620	-	TPM	Suicide events	Increased risk for GBP, LTG, OXC, TGB, VPA	+	+	-	Demographics and large list of medical factors
Andersohn et al. 2010 [11]	Case-control	44,300	+	No ASM	Suicide events	Increased risk for LEV, VGB, TGB, TPM	-	+	-	Type of epilepsy, use of benzodiazepines, and psychiatric disorders
Arana et al. 2010 [3]	Case-control	5,130,795 (Epilepsy 39,325)	±(subgroup)	No ASM	Suicide events	No increased risk for epilepsy	+	+	-	Age, duration of illness, AED use, drugs for psychiatric disorders, psychiatric disorders, alcohol abuse and chronic disease score
Gibbons et al. 2010 [4]	Cohort GBP	131,178	-	Exposed vs no exposed	Suicide attempts	No increased risk	-	-	-	Demographic and medical factors
Pugh et al. 2012 [13]	Cohort (VA >65 yo new users)	2,430,286 (90,263 exposed to AEDs)	-	Exposed vs no exposed	Suicide events	Increased propensity score for GBP, PHT, LTG, LEV, TPM, VPA	-	-	-	Demographic and medical factors
Pugh et al. 2013 [5]	Cohort (>65 yo VA)	90,263	-	No drug (before and after exposure)	Suicide related behavior	No increased risk	-	-	-	Demographic and medical comorbidities
Josephson et al. 2018 [6]	Cohort study (first prescription)	7,400	+	No drug (hazard of a first ever code after first ASM prescription)	Psychiatric symptoms	No increased risk	-	+	-	Age, gender, PHx psychiatric disorders
Raju Sagiraju et al. 2018 [12]	Cohort (VA) monotherapy (mono users)	22,282 (255 epilepsy)	± (subgroup)	No Drug (ASMs users with epilepsy vs ASMs w/0 epilepsy vs non ASM users	Suicide-related behaviors	Peak of suicide behavior around ASM prescription	-	-	-	Sociodemographic factors and health comorbidity
Dreier et al. 2019 [14]	Case-control (suicides vs controls)	1,759	-	No drug (current vs. prior use ASMs)	-	Increased risk current vs previous use Increased risk for PB exposure 1.26 (95%CI 1.13–1.40) PB	PHx+ 1.28 95%CI 1.07–1.54 PHx- 1.26 95%CI 1.11–1.43	PHx + 1.48 95%CI 1.18–1.87 PHx- 1.21 95%CI 1.07–1.35	-	Sociodemographic
Klein et al. 2021 [7]	Meta-analysis Phase 2 and 3 studies	5,996	+	Eslicarbazepine, perampanel, Brivaracetam, cannabidiol, cenobamate vs placebo	Suicidality (ideation, attempt, completed)	No increased risk for suicide or suicidal ideation vs placebo	-	-	+CSSS	-

+ = present; - = not present; ASM = antiseizure medication; CBZ = carbamazepine; LTG = lamotrigine; LEV = levetiracetam; VPA = valproate; TPM = topiramate; GBP = gabapentin; PGB = pregabalin; PHT = phenytoin; CLB = clobazam; OXC = oxcarbazepine; TGB = tiagabine; PB = phenobarbital; PHx = past history; CSSS = Columbia Suicidal Severity Scale

and poor access to mental health care with consequent worsening of the underlying mental health problem [21] Many studies have pointed out that the neurobiological changes and network abnormalities seen in people with epilepsy, especially temporal lobe epilepsy, are very similar to those seen in suicide victims [22]. These changes represent the biological basis for the well-known bidirectional relationship between epilepsy and suicide and for the observation that suicide is more frequent in epilepsy even in the absence of a psychiatric comorbidity [23]. The bidirectional relationship between epilepsy and suicide was re-investigated in the light of the FDA alert in a recent retrospective population-based cohort study in 14,059 UK patients with incident epilepsy age 10–60 [24]. This study clearly shows that suicide attempts and recurrent suicide attempts are associated with epilepsy even before ASMs are started [24]. These findings would clearly suggest a relationship between epilepsy and suicide rather than with ASMs, and the observed association with ASMs would just represent an epiphenomenon of having epilepsy. This would also explain why the FDA meta-analysis reported such an increased risk in people with epilepsy and not in people with conditions other than epilepsy taking ASMs.

3.2. Psychiatric contributors to suicide in epilepsy: not just a matter of medications

A number of authors have investigated psychiatric contributors to suicide in epilepsy and data available support the notion that these contributors are far more relevant than ASMs. The pattern of psychiatric disorders and not being in remission represent well-known risk factors.

A retrospective chart analysis using data from the Veterans Philadelphia Medical Center points out that a previous history of substance use and not ASMs prescription is significantly associated with suicidal ideation [25]. This is entirely in keeping with the psychiatric literature outside epilepsy showing that a diagnosis of substance abuse significantly increases the suicide risk in any psychiatric disorder [26].

A prospective case-control study of 506 adults with incident suicidal attempt, recruited in suicide treatment centers in France compared with 2,829 matched controls from primary care settings, investigates, among different factors, also medication use, including ASMs, in the 12 months before the suicide, using a standard telephone interview. The authors show no significant association with ASMs use (1.5 95% CI 0.9–2.4), while active depression is the main risk factor (1.6 95% CI 1–2.5) [27].

The lack of association with ASMs, as compared to the presence of depression, has been replicated at a cross-cultural level. A cross-sectional study of 251 patients with epilepsy in rural China using the Mini International Neuropsychiatry Interview (MINI) shows that a previous history of depression and poor family relationship are associated with suicide rather than ASMs prescription [28].

An interesting point made by studies in this area is the association with self-poisoning. This was already reported in old studies, particularly the association with barbiturates [17]. High rates of self-poisoning have been confirmed by a more recent study showing that people with epilepsy are twice as likely to poison themselves as compared to controls (38% vs. 17%) [29]. The association with barbiturates was also mentioned in one of the more recent studies on ASMs and suicide [14]. However, it has to be acknowledged that the association with phenobarbital may be probably due to the very high lethality of overdose as compared to other ASMs. This seems to be further confirmed by a recent population-based cohort study using primary care data linked to hospitalization and mortality records in the UK that shows that medication poisoning, either intentional or unintentional, is more frequent in epilepsy than in the general population but drug classes involved include opioids (56% 95% CI 43.3–69.) and psychotropic medications (32.3% 95% CI 20.9%–45.3%) while ASMs are less involved (9.7% 95% CI 3.6%–19.9%) [30]. This would support the hypothesis that the association with a specific medication may be due to the potential lethality rather than the psychotropic potential. Comparative data on the lethality potential of ASMs in overdose are almost non-existent. A retrospective cross-sectional analysis of 74,818 ASM exposure cases in pre-teens and adolescents shows that tiagabine and carbamazepine are those with the greatest odds of a serious outcome, ORs 4.7 95% CI 3.6–6.3 and 3.1 95% CI 2.8–3.4, respectively, while those with the lowest odds of a serious outcome are gabapentin and clonazepam [31]. Barbiturates were not included in this study.

3.3. The relative contribution of antiseizure medications

All data presented so far seem to suggest that a number of factors other than ASMs contribute to suicide in epilepsy. However, there is no doubt that ASMs are associated with psychiatric side effects, such as depressed mood, aggressive behavior, anxiety, and psychosis [20,32]. It is, therefore, possible to speculate that the development of such adverse effects in people with an already preexisting psychiatric disorder may represent a precipitating factor.

A retrospective review of medical records of 4,085 adults with epilepsy recently started on ASMs and followed in an epilepsy center in the US show that one in six patients develops psychiatric side effects and 0.17% suicidal ideation [33].

Many clinicians have the perception that some ASMs, such as sodium channel blockers, are less problematic than others. A cohort study from Canada looking at psychiatric symptoms after the first ASM prescription shows that carbamazepine and lamotrigine are associated with lower hazard of any coded psychiatric symptom or disorder as compared to clobazam, levetiracetam, phenytoin, topiramate, and valproate [6]. However, there are no robust head-to-head comparison trials providing strong evidence for the supposed safety of some ASMs and for this reason, clinicians should bear in mind that psychiatric side effects can happen with any drug in predisposed individuals. In this scenario, periodic screening, identification of comorbidities, and close clinical monitoring represent the most appropriate strategy. A case-control study in 6,880 patients with epilepsy shows that suicide is associated with inadequate follow-up and points out that psychiatric comorbidities are not necessarily severe [34]. It is, therefore, crucial to be vigilant and to routinely screen

patients with epilepsy for depression, anxiety, and suicide ideation. This point is still completely ignored by the majority of clinicians and despite lots of discussion about the FDA alert, clinical practice of neurologists does not seem to have changed dramatically. A survey of neurology practitioners in the U.S.A. in 2009, 1 year after the FDA warning, showed that 62% did not use clinical instruments to routinely screen for depression, 42% did not feel comfortable with initiating any treatment for mood and anxiety disorders, 98% mentioned psychiatric adverse events to their patients but only 44% warned them about suicide behavior. Quite worrying, more than 50% were not aware of whether their patients ever attempted to commit suicide and 46% of clinicians felt the FDA alert was not going to change their practice [35].

4. Conclusion

After an explosion of research shortly after the FDA warning was released, only a limited number of studies were published in more recent years, and they did not overcome the limitations of previous studies. Overall, available literature does not support an obvious causal relationship between ASMs and suicide. On the contrary, studies are highlighting the complex relationship between suicide and epilepsy, strengthening the bidirectional relationship and the multifactorial origin.

5. Expert opinion

There is no doubt that the FDA alert has brought to light the issue of suicide in epilepsy and has promoted research in this area. Unfortunately, this seems to have had only a limited impact on clinical practice as still many patients are not routinely screened for psychiatric disorders and, most importantly, suicide is still ignored by neurologists and neurology practitioners in their consultations. This is due to the stigma behind suicide in general, the lack of training of neurologists and healthcare professionals dealing with people with epilepsy about how to manage suicide and mood disorders, the lack of user-friendly clinical instruments, and finally the lack of integrated clinical pathways in neurology and psychiatry. There is no doubt that further research in this area is needed.

A better understanding of the relationship between epilepsy and suicide will ultimately lead to clinical programs and clinical instruments for this purpose with screening instruments and risk assessment protocols for suicide in epilepsy. Such data will be able to clarify the relative role of ASMs as a contributing factor for suicide in epilepsy. Barriers to studies in this area include the low frequency of the phenomenon requiring a large sample size and the costs connected to prospective studies. In order to overcome these limitations, many researchers identified patients through prescription or insurance databases but these studies are limited by the low diagnostic accuracy and the low level or clinical definition that will be essential to advance further in this area.

Conversely, data on suicidality are now collected routinely in regulatory trials of ASMs. Such data will allow the identification of compounds that may require more close monitoring when approved and marketed with the development of more Phase 4 studies on this subject. Data coming from regulatory trials are of limited importance as high-risk patients are usually excluded but it is a good starting point to identify high-risk compounds.

The development of clinical pathways as well as risk assessment protocols will allow a much safer use of ASMs in people with epilepsy. In fact, trailing any ASM in a safe environment is much more beneficial for patients than just choosing a low-risk ASM in an unsafe environment because in this way patients are deprived of potentially good options that may make them seizure free and, as already stated, predisposed individuals can develop psychiatric side effects with any drug. In fact, even if some ASMs seem to be more frequently associated with suicide behaviors, than others, it is important to shift the paradigm of clinicians from the drug to the patient. Neurologists need to become competent in identifying predisposed, high-risk individuals and to have protocols to minimize risks rather than just actively avoiding some ASMs because this is easy and convenient.

In 5 years, there will be clinical instruments validated for people with epilepsy and hopefully validated risk assessment tools and potential pathways needing implementation. New ASMs will have already information on suicidality when marketed and these will be further investigated in open-label extension and Phase 4 trials. The alert on increased suicidality risk will be still present in the information leaflet of ASMs but hopefully with a better understanding from patients and their neurologists.

Declaration of interests

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Reviewer disclosures

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