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Suicidality associated with anti-epileptic drugs: implications for the treatment of neuropathic pain and fibromyalgia

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Keywords

Suicide; Suicidal ideation; Suicidality; Antiepileptic drugs; Neuropathic pain; Fibromyalgia

1. Introduction

Anti-epileptic drugs (AEDs) have a prominent role in the treatment of several types of chronic pain. Gabapentin and pregabalin are recommended as first-line treatments for various neuropathic pain conditions, carbamazepine and oxcarbazepine are commonly used in trigeminal neuralgia, and certain AEDs are considered second- or third-line treatments for neuropathic pain [3,7,11,12,25]. In addition, pregabalin is recommended for fibromyalgia

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[8], and topiramate and valproic acid are considered first-line treatments for migraine prophylaxis [13,33].

Given the role played by AEDs in pain treatment, it is important to consider recent research and recommendations regarding AEDs and suicidality, which includes both suicidal behavior and suicidal ideation [17,31,37]. On the basis of a meta-analysis, the U.S. Food and Drug Administration (FDA) concluded that AED treatment for any indication is associated with an increased risk of suicidality [37]; as a consequence, AED product information was changed to include warnings about this risk. After conducting an independent review, the European Medicines Agency (EMA) also instituted warnings about AEDs and suicidality [22,27].

In evaluating the risk of suicidality associated with AEDs, an important consideration is that several conditions for which they are prescribed also have an increased suicide risk, including epilepsy [10,20] and certain psychiatric disorders [6,14,21]. Chronic pain is also associated with suicidality [32,34,36], and as many as 50% of patients with chronic pain have comorbid depression [5], a well-established risk factor for suicide [9].

The objective of this article is to review recent research on suicidality and AEDs and to discuss its implications for the treatment of neuropathic pain and fibromyalgia. The role of AEDs in migraine treatment, which is prophylactic rather than symptomatic, is beyond the scope of this review, as is AED treatment in seizure disorders and in psychiatric conditions for their mood stabilizing effects.

2. Methods

A Medline search exploding the MESH terms “suicide” and “anti-convulsants” and a PubMed search were conducted. Studies included in this review were generally limited to those that appeared in 2008 and after and considered relevant to FDA and EMA warnings. Separate searches were performed to gather data from FDA, EMA, and other sources. Relevant studies are discussed below and summarized in Table 1.

3. Results

The FDA conducted a meta-analysis that focused on 199 placebo-controlled trials of 11 AEDs. The treatment groups contained a total 27,863 patients and the placebo groups contained 16,029 patients [37]. Approximately 25% of these patients had epilepsy, 27% had psychiatric disorders, including mood disorders and schizophrenia, and 48% were classified as having “other” conditions, including obesity, insomnia, migraine, and various pain disorders. The Columbia Classification Algorithm of Suicide Assessment was used for retrospectively assessing suicidal behavior and ideation [31]. Based on adjusted risk estimates, 0.43% of patients in the AED groups had suicidal behavior or ideation vs. 0.24% in the placebo groups. The FDA concluded that AEDs appeared to increase the risk of suicidality regardless of treatment indication, specific AED, or mechanism of action, and that increased risk was observed as early as one week after treatment initiation and continued for at least 24 weeks. When treatment indications were assessed individually, the only group with a significantly increased risk was epilepsy patients, for whom the odds ratio

was 1.80 (95% confidence interval = 1.24, 2.66). However, the odds ratio for the “other” group in the FDA meta-analysis, which included patients with various pain conditions, was 1.87 (95% confidence interval = 0.81, 4.76) (Table 1); patients in this group were taking divalproex, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, topiramate, or zonisamide. As discussed below, methodological limitations of the adverse event data used in this study hamper the ability to draw causal inferences.

Olesen et al. [28] conducted an analysis of 6,780 suicides and a cohort study of 169,725 treatment-naïve patients in Denmark. The cohort population consisted of patients with epilepsy, psychiatric disorders, and those taking opioids, presumably for chronic pain. The authors concluded that clonazepam, valproate, lamotrigine, and phenobarbital may increase the risk of suicide shortly after treatment initiation.

Paterno et al. [29] conducted a cohort study of 297,620 patients treated for various neurologic and psychiatric conditions using a medical claims database. Suicidal acts and violent death were compared in patients beginning AEDs and those taking topiramate, the reference AED. Cox proportional hazards models and propensity score analyses demonstrated that several AEDs, including gabapentin, increased the risk of suicidal acts. Of note, 16.8% of the gabapentin group was being treated for neuropathic pain whereas less than 1% was treated for epilepsy.

Considered together, these three studies provide evidence consistent with an increased risk of suicidality in patients taking AEDs for pain conditions [28,29,37]. However, two other studies examining such patients did not find evidence of increased risk. VanCott et al. [39] assessed suicide-related behaviors in 64 older male patients who received AEDs and 768 matched controls. This study had a high percentage (85.7%) of patients previously diagnosed with chronic pain and the association between AED treatment and risk of suicidality was not significant. On the basis of a study examining the relationship between gabapentin and suicide attempts in 131,178 patients with epilepsy, pain, or various psychiatric disorders, it was concluded that gabapentin did not increase the risk of suicide attempts in the patients with epilepsy or pain [16].

Several other studies evaluated the association between AEDs and suicidality but did not examine pain patients. In 163 patients with epilepsy, AEDs did not worsen mood or increase suicidal ideation, although the subgroup of patients who increased their AED dosage had a significant increase in new suicidal ideation [40]. A study of 44,300 patients from the U.K. identified cases of self-harm or suicidal behavior with current, recent, and past use of AEDs in those with afebrile seizures or epilepsy [1]. It was concluded that risks were three times higher in patients taking newer AEDs. In another U.K. study, suicide attempts and completions were assessed in over five million patients treated with AEDs [2]. The authors concluded that AEDs increased the risk of suicide-related behaviors in patients with depression and in those who did not have epilepsy, depression, or bipolar disorder. Finally, the risk of suicide attempts was not increased in bipolar disorder patients receiving AEDs in a medical claims database [15].

4. Limitations

The results of the studies discussed above are inconsistent – in patients with epilepsy and other conditions and also in those with chronic pain – with several supporting FDA and EMA conclusions that AEDs are associated with an increased risk of suicidality and others finding no evidence of such a risk. Unfortunately, the number of studies is too small, and the differences among them are too great, to make it possible to explain the differences in their results. The inconsistent results may be accounted for by several factors, including variability in research designs, control or comparison groups, and sample sizes. In addition, these retrospective studies differed with respect to which covariates were included to address confounding by indication and other potentially important baseline demographic and clinical factors.

There is also variability among the studies with respect to the suicidality outcomes examined. Some only assessed a specific component of suicidality, for example, suicide attempts or completions but not ideation. To ensure more complete and timely prospective evaluation in clinical trials of interventions that might increase suicidal ideation and behavior (e.g., drugs with CNS effects), the FDA recently released a revised draft guidance [38] that adopted and recommends classifying suicidal ideation and behavior into the 11 standard categories from the Columbia-Suicide Severity Rating Scale (C-SSRS) [30] (Table 2).

Another important source of variability that might account for inconsistency in results is that AEDs are used to treat multiple disorders, each of which carries its own risk for suicidality, including chronic pain. It is possible that AEDs only increase the risk of suicidality in subgroups of patients with a disorder — for example, patients with chronic pain who have comorbid major depression, or specific epilepsy types — which will only be revealed by careful evaluations of primary and comorbid diagnoses accompanied by prospective suicidality assessments.

It is also important to consider that individual AEDs might have different risks of suicidality, as some but not all of the studies reviewed above suggest. AEDs appear to differ in the extent to which depression occurs as a treatment-related adverse event [26], and some AEDs are used as “mood stabilizers” and can improve depression and impulse control in certain psychiatric disorders [14,19,21]. To the extent that different AEDs either cause or ameliorate depression, it would not be surprising if their risks of suicidality also differ.

Existing studies of AEDs and suicidality have generally been either retrospective analyses of completed clinical trials or cohort and case-control studies. Such secondary analyses and observational studies can provide important hypotheses regarding causal relationships. However, conclusions regarding causality must remain preliminary until results of prospectively designed randomized clinical trials, epidemiologic studies, and administrative surveys converge in showing that one or more AEDs are causally associated with an increased risk of suicidal ideation, behavior, or completed suicide [23,24].

Specifically with respect to the FDA meta-analysis [37], Hesdorffer and Kanner [18] argued that there was an inadequate number of events and limited statistical power. In addition,

although the test of heterogeneity conducted by FDA among AEDs was not significant and 8 of 11 drugs were associated with increased suicidality, the results were significant for only lamotrigine and topiramate.

5. Conclusions

Despite its limitations, the literature reviewed in this article suggests that the risk of suicidality — although small in absolute terms — should be considered carefully in the treatment of patients with neuropathic pain, fibromyalgia, and other chronic pain conditions for which treatment with an AED is being considered. The risk of suicidality can be evaluated in patients initiating AED treatment and periodically during treatment, and would be especially appropriate in those with evidence of past or current suicidality, past or present mood disorders, and other risk factors for suicidality [34], including treatment with antidepressant medication in individuals under the age of 25 [35].

Given that chronic pain is a risk factor for suicide, clinicians who evaluate and treat pain must recognize early signals of suicidality and should consider tracking patients' mental status in relation to suicidal ideation and behavior just as they would pain severity or vital signs. Although several measures of suicidality are available, the only one specifically described as adequate for this purpose by FDA [38] and expert consensus [23,24] is the C-SSRS, available in over 100 languages and used internationally across numerous healthcare systems, including multiple U.S. states [30; http://cssrs.columbia.edu/about_cssrs.html]. The C-SSRS can improve care through providing criteria for next steps (e.g., referrals), in turn facilitating triage, redirecting resources, and facilitating care delivery to those at highest risk. Importantly, one of the main benefits of its use in clinical trials is helping avoid false signals (which are common in adverse event data), potentially limiting false positives while identifying those at highest risk. For example, a recent study reported that 6.2% of patients screened positive with the C-SSRS whereas 23.8% screened positive with the PHQ-9 [Ralston L, Katzan I, Viguera AC, Patient satisfaction with an electronic suicide screening using the Columbia Suicide Severity Rating Scale in an outpatient psychiatry clinic. American Psychosomatic Society, Atlanta, Georgia, November 15, 2012]. Due to its ability to predict suicide attempts, the C-SSRS not only can decrease unnecessary treatment referrals and exclusions but also can identify patients who would have been missed using other methods.

In deciding whether to initiate or continue AED treatment in chronic pain patients, especially those with risk factors for suicidality (beyond the increased risk conferred by having chronic pain), careful evaluation is necessary to determine whether treatment benefits outweigh risks. The effectiveness, safety, and tolerability of other pharmacologic and non-pharmacologic treatments that have not been associated with increased suicidality should be taken into account in this benefit-risk assessment. Although the benefits of AED treatment in epilepsy generally outweigh the risk of treatment-emergent suicidality [4], such an overall evaluation has unfortunately not been conducted for patients with chronic pain.

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Table 1

Study characteristics

Study	Indications for AED treatment	Sample size	Comparison group; sample size	Research design	Outcome measures	Key results
Andersohn et al. [1]	Afebrile seizures; epilepsy	Cohort: 44,300; cases: 453	Controls matched on age and sex: 8,962	Nested case-control	Self-harm; suicidal behavior	Newer AEDs had a 3-fold increased risk of self-harm and suicidal behavior compared with no use of AEDs during the past year; OR = 3.08 (CI: 1.22, 7.77).
Arana et al. [2]	Epilepsy; depression; bipolar disorder	5,130,795		Cohort with case-control component	Suicidal acts; completed suicides	The use of AEDs was not associated with an increased risk of suicide-events in patients with epilepsy or bipolar disorder, but was significantly associated with an increased risk in patients with depression and in those who did not have epilepsy, depression, or bipolar disorder.
Gibbons et al. [15]	Bipolar disorder	Patients who received one of 11 AEDs: 13,385	Patients who did not receive one of the AEDs or lithium: 25,432	Cohort	Suicide attempts	No significant difference in rates of suicide attempts for patients treated with an AED vs. patients not treated with an AED or lithium (both groups, 13/1000 PY).
Gibbons et al. [16]	Epilepsy; pain disorders; bipolar disorder; major depressive disorder; schizophrenia; other psychiatric disorders	131,178		Cohort	Suicide attempts	No significant difference in suicide attempt rates before (3.48/1000 PY) vs. after (3.45/1000 PY) gabapentin treatment. Significant reductions in suicide attempt rates were seen for bipolar disorder, major depressive disorder, and other psychiatric disorders.
Olesen et al. [28]	Epilepsy; psychiatric; other	Case-crossover: 6,780; AED treatment-naïve cohort: 169,725		Case-crossover; cohort	Completed suicides	In a case-crossover analysis, AED treatment initiation increased the risk of suicide; OR = 1.84 (CI: 1.36, 2.49), with clonazepam, lamotrigine, phenobarbital, and valproate each significantly associated with an increased risk. The results of the cohort analysis were similar, with several AEDs significantly associated with an increased risk compared to carbamazepine monotherapy.
Patormo et al. [29]	Various neurologic and psychiatric conditions	239,767	Patients taking topiramate: 57,853	Cohort	Completed suicides; suicide attempts; violent deaths	Compared with topiramate, the risk of suicidal acts was increased for gabapentin (HR = 1.42; CI: 1.11, 1.80), lamotrigine (HR = 1.84; CI: 1.43, 2.37), oxcarbazepine (HR = 2.07; CI: 1.52, 2.80), tiagabine (HR = 2.41; CI: 1.65, 3.52), and valproate (HR = 1.65; CI: 1.11, 2.37).

Study	Indications for AED treatment	Sample size	Comparison group; sample size	Research design	Outcome measures	Key results
U.S. FDA [37]	Epilepsy; psychiatric; other	27,863	Placebo: 16,029	Meta-analysis	Completed suicides; suicidal attempts; preparatory acts toward imminent suicidal behavior; suicidal ideation	1.25, 2.19). Results were similar when violent deaths were included. 1.25, 2.19). Results were similar when violent deaths were included.
U.S. FDA [37]	Epilepsy; psychiatric; other	27,863	Placebo: 16,029	Meta-analysis	Completed suicides; suicidal attempts; preparatory acts toward imminent suicidal behavior; suicidal ideation	Estimated OR of an AED patient experiencing suicidal ideation or behavior vs. placebo patient was 1.80 (CI: 1.24, 2.66). There were 1.9/1000 (CI: 0.6, 3.9) more AED than placebo patients who experienced suicidal ideation or behavior.
VanCott et al. [39]	Any new prescription for AED monotherapy	64	Matched controls: 768	Case-control	Suicidal ideation; suicidal behavior	Strongest predictor of suicidal ideation and behavior based on logistic regression was affective disorder diagnosed before AED treatment; OR = 4.42 (CI: 2.30, 8.49). Increased suicidal ideation and behavior were not associated with individual AEDs.
Wen et al. [40]	Epilepsy	Change in AED treatment: 92	No AED change: 71	Retrospective cohort	Mood disorders; suicidal ideation	Significant improvements in depression and suicidal ideation were seen for the "no AED change group." Only the "AED dose increased group" had significantly increased onset of new suicidal ideation compared to the "no AED change" group (11% vs. 6%, p = 0.05).

AED = anti-epileptic drug; CI = 95% confidence interval; FDA = Food and Drug Administration; HR = hazard ratio; OR = odds ratio; PY = person years.

Table 2**Suicidal ideation and behavior categories and definitions [30,38]**

Suicidal ideation	
Passive suicidal ideation: wish to be dead	
<ul style="list-style-type: none"> Patient has thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. 	
Active suicidal ideation: nonspecific (no method, intent, or plan)	
<ul style="list-style-type: none"> General nonspecific thoughts of wanting to end one's life or commit suicide (e.g., "I've thought about killing myself") without general thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. 	
Active suicidal ideation: method, but no intent or plan	
<ul style="list-style-type: none"> Patient has thoughts of suicide and has thought of at least one method during the assessment period. This situation is different than a specific plan with time, place, or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, "I thought about taking an overdose but I never made a specific plan as to when, where, or how I would actually do it...and I would never go through with it." 	
Active suicidal ideation: method and intent, but no plan	
<ul style="list-style-type: none"> Active suicidal thoughts of killing oneself, and patient reports having <u>some intent to act on such thoughts</u>, as opposed to "I have the thoughts but I definitely will not do anything about them." 	
Active suicidal ideation: method, intent, and plan	
<ul style="list-style-type: none"> Thoughts of killing oneself with details of plan fully or partially worked out and patient has some intent to carry it out (i.e., some degree of intent is implicit in the concept of plan). 	
Suicidal behavior	
Completed suicide	
<ul style="list-style-type: none"> A self-injurious behavior that resulted in fatality and was associated with at least some intent to die as a result of the act. Evidence that the individual intended to kill him- or herself, at least to some degree, can be explicit or inferred from the behavior or circumstance. 	
Suicide attempt	
<ul style="list-style-type: none"> A potentially self-injurious behavior, associated with at least some intent to die as a result of the act. Evidence that the individual intended to kill him- or herself, at least to some degree, can be explicit or inferred from the behavior or circumstance. A suicide attempt may or may not result in actual injury. 	
Interrupted suicide attempt	
<ul style="list-style-type: none"> When the person is interrupted (by an outside circumstance) from starting a potentially self-injurious act (if not for that, actual attempt would have occurred). 	
Aborted suicide attempt	
<ul style="list-style-type: none"> When person begins to take steps toward making a suicide attempt, but stops before actually engaging in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops before being stopped by something else. 	
Preparatory acts toward imminent suicidal behaviors	
<ul style="list-style-type: none"> This category can include anything beyond a verbalization or thought, but it stops short of a suicide attempt, an interrupted suicide attempt, or an aborted suicide attempt. This might include behaviors related to assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). 	
Self-injurious behavior without suicidal intent	
<ul style="list-style-type: none"> Self-injurious behavior associated with no intent to die. The behavior is intended purely for other reasons, either to relieve distress (often referred to as <i>self-mutilation</i> (e.g., superficial cuts or scratches, hitting or banging, or burns)) or to effect change in others or the environment. 	