AN UPDATE ON ANTIEPILEPTIC DRUGS AND SUICIDE: ARE THERE DEFINITIVE ANSWERS YET?

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In 2008, the Food and Drug Administration (FDA) issued a warning that any and all antiepileptic drugs (AEDs) might increase the risk of suicidal ideation, suicide attempt, and completed suicide. Considerable confusion and concern followed regarding the use of these drugs, in general, and specifically for people with epilepsy. Recently, four publications examined suicidality and AED use among several databases and illustrated how biases affect the findings. None of the studies was able to control completely for the indication for which the AEDs were prescribed or to account for the varying intensities with which different specialists monitoring patients for suicidality. Though multiple analyses were conducted for many AEDs, no study controlled for the numerous comparisons made. The result is a multitude of contradictions in the findings across studies and even within studies, with no study providing clear or convincing support for the FDA conclusions. This review attempts to clarify the methodological issues in assessing potential associations between AED use and suicidality.

The lifetime prevalence of suicide is estimated to be around 1.1 to 1.2 percent in the general population of the United States (1), while the prevalence of suicide attempts ranges between 1.1% and 4.6% (2,3). Primary mood disorders, schizophrenia, antisocial and borderline personality disorders, as well as substance abuse are the psychiatric disorders most commonly associated with completed suicide risk (4,5). The relationship between suicidal risk and individual psychiatric comorbidities is a complex one. For example, the relation between suicidality and bipolar disorders includes: 1) the phase of the illness, with almost 80% of suicide attempts occurring in the midst of a major depressive episode; 2) younger age of onset of the bipolar disorder, defined as a younger age at the first episode of depression or mania; 3) development of rapid cycling bipolar illness, defined as four or more depressive and/or manic (or hypomanic) episodes in a 12-month period; 4) other comorbid psychiatric disorders, including a history of alcohol or substance abuse, anxiety disorders, and personality disorders (6). Furthermore, suicidality is not a onetime event. Following a first episode, the risk is substantially increased for subsequent episodes, including completed suicide. For example, one study found that 10 to 20 percent of patients who report a suicide attempt successfully committed suicide within 10 years (7).

Several AEDs (e.g., valproic acid, carbamazepine, oxcarbazepine, and lamotrigine) have been extensively used as mood stabilizing agents for patients with bipolar disease. Yet, the prophylactic efficacy of these AEDs specifically for prevention of suicidality has been limited to comparing valproic acid and carbamazepine against the gold standard, which is lithium (8,9). In these studies, valproic acid and carbamazepine were not as efficacious as lithium for preventing suicide. This finding does not mean that they are ineffective as mood stabilizers, nor does it mean that they act to increase the risk of suicidality relative to no treatment or to other treatments.

Epilepsy, itself, is also associated with a relatively high suicide risk (10). One meta-analysis of 21 reports of death among epilepsy patients found that 11.5% of the deaths were attributed to suicide (11). As in the case of bipolar disorder, the relationship between epilepsy and suicidal risk is complex. The operant variables include: 1) the existence of a current and/or past psychiatric disorder, particularly affective disorder, which raises the risk of completed suicide by 19-fold (12); 2) a history of suicide attempt (13); 3) the type of epilepsy (i.e., higher frequency in temporal lobe epilepsy); 4) the existence of postictal psychiatric disturbances (10,14); 5) an increased risk for psychosis following acute withdrawal of AEDs (15); and 6) exposure to some AEDs that can trigger psychiatric disturbances, facilitating the development of suicidal behavior (15). Individuals who have attempted suicide in the past have a five-fold higher risk of developing epilepsy (16). The complex relation between epilepsy and suicidal risk was reviewed previously in this journal (17).

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Despite the relatively high prevalence of psychiatric comorbidities, and in particular, the increased suicidal risks associated with epilepsy, clinicians seldom identify and refer these patients for psychiatric treatment. It is also rare for patients and family members to spontaneously report the existence of psychiatric disturbances. This pattern appears to have changed since 2008, when the Food and Drug Administration (FDA) issued a warning that any and all AEDs might increase the risk of suicidal ideation, suicide attempt, and completed suicide (suicidality) (18). The warning resulted in considerable confusion and concern about the use of these drugs for the general population but particularly for people with epilepsy. The methodological inadequacies of the FDA analysis previously have been discussed (19).

Surprisingly, little data exist in the literature on the association between AEDs and suicidality. Psychiatric adverse events that can lead to an increased suicidal risk have been identified more frequently with AEDs that have GABAergic properties, particularly in vulnerable patients, such as those with a psychiatric history or a family psychiatric history (20–23). The AEDs with GABAergic properties include the barbiturates, the benzodiazepines, tiagabine, vigabatrin, topiramate, zonisamide, and gabapentin. The rise in depression and, in particular, in suicidal behavior has been attributed to a GABAergic-mediated decrease in serotonin secretion at the raphe nuclei (24–26). Other AEDs without known GABAergic effects, such as levetiracetam, have also been associated with an augmented incidence of psychiatric adverse events that can lead to increased suicidality, but the potential pathogenic mechanisms remain to be established (21).

Recently, four publications have examined suicidality and AED use in epidemiological analyses of administrative databases (27–30). The following review presents a methodological analysis and critique of these studies, a summary of the conclusions that might be drawn from the four together, and some thoughts on how the findings might or might not influence clinical practice. Before discussing specific aspects and results of these studies, however, a summary of key methodological considerations that need to be taken into account when reading this literature is delineated.

Methodological Considerations

The ideal study design for testing cause–effect relationships is a randomized experiment or trial. In this case, there are 15–20 drugs that would need to be tested, optimally against placebo. A valid standardized psychiatric assessment, administrated prior to initiating treatments and then throughout the follow-up period, would be essential in order to verify outcomes and overcome problems associated with using spontaneous reporting of adverse events to determine suicidality. The outcome of suicide attempt and completed suicide is relatively rare, and the number of patients that would be needed to have adequate power to rule out a clinically significant increase in suicide risk for each drug would be prohibitive in terms of cost and time. Furthermore, as the purpose of performing such a large study would be to determine if a treatment caused harm, the study might be considered unethical in the face of the FDA warning. In addition, it might be difficult to enroll people in the trial.

In the absence of such trials, observational studies are often performed using existing datasets. Although such studies can produce results fairly rapidly, they are complicated to do well and always leave doubt regarding the validity of their findings and the extent to which causal inferences can be drawn from them. For a rare outcome, such as suicidality, it is convenient to make use of large administrative databases from insurance companies and health plan providers as well as record-linkage systems available in some settings. These databases provide the necessary sample size; however, study population is only the first of many considerations needed to understand this complex relationship.

In studying suicidality as it may be related to AED use, the following are some of the critical features that must be addressed in design, analysis, and interpretation of nonrandomized studies. 1) A history of psychiatric disorders and most especially of suicide attempts is the single greatest risk factor for future suicide attempt and completed suicide. The risk for recurrent suicide attempt and complete suicide is high over an 8-year period, a 28 to 30 percent risk for recurrence and, as previously noted, a 5 to 10 percent risk for completed suicide in people hospitalized for their first suicide attempt (31,32). The risk of a subsequent completed suicide remains elevated for years after the initial suicidal episode, with approximately two-thirds of repeated attempts resulting in death occurring at least 15 years after the initial attempt in people hospitalized for self-poisoning (32). These data underscore the importance of measuring the history of suicide attempt in all patients, independent of treatments received, as well as the necessity of using this information in the design or analysis of the study, or both. 2) Drugs are selected or avoided for specific reasons, depending upon the clinical profile of each person, which often leads to what is commonly called "confounding by indication." Because of concerns regarding mood disorders that have been associated with some AEDs (e.g., phenobarbital, primidone, topiramate, zonisamide, vigabatrin, tiagabine, and levetiracetam), it is likely that knowledge of a patient's psychiatric history, including suicide attempts, would influence a physician's tendency to prescribe those drugs. In an extreme situation, nobody with a history of suicidality might be prescribed topiramate, and instead, all such patients might receive AEDs with mood stabilizing properties, such as lamotrigine, carbamazepine, oxcarbazepine, or sodium valproate, depending on the

electroclinical syndrome and type of seizure. Comparing lamotrigine to topiramate would thus result in a comparison of a group of patients with a known high risk of suicide to a group with a known low risk, which could yield a finding suggesting that lamotrigine increased the risk of suicidality relative to topiramate. This outcome, of course, is the opposite of what is seen in randomized trials and in clinical experience. 3) Knowledge of a patient's past suicidal episodes may influence the intensity with which a physician monitors for future episodes. Thus, in the example above, those patients with a history of suicidality would be more carefully monitored. In this situation, not only would the high-risk patients be disproportionately represented in the lamotrigine group, any suicidal tendencies in that high-risk group would more likely be identified, thus increasing any apparent difference with the referent group. Such a study design can result in detection or diagnostic suspicion bias. 4) The efficacy of the AEDs with mood stabilizing properties for the prevention of suicidality has yet to be demonstrated in controlled trials. 5) Interpretation of increased suicidal attempts and completed suicides in patients treated with mood stabilizing AEDs should not presume that these agents increase a suicidal risk but rather may reflect their lack of efficacy in preventing suicide. 6) Suicidality involves a range of outcomes, from thinking about killing one's self to completed suicide. Drugs are started for specific reasons. If the reason for starting a drug at a particular point in time is for treatment of a suicidal or other psychiatric episode, drug initiation may mark the beginning of a particularly high-risk period, without the drug, itself, actually being the factor that increases the suicide risk. This fact will not easily be reflected in administrative databases. With these points in mind, the four studies are evaluated; their methodological features with respect to the above considerations are summarized in Table 1 and their results are highlighted in Table 2.

Gibbons et al.

The study by Gibbons et al. is restricted to the association between AEDs and suicide attempt in newly diagnosed bipolar disorder and is the only one of the four papers to focus on a single underlying condition (27). These authors used the

TABLE 1. *Comparison of Methodological Features in Four Studies of AEDs and Suicidality*

VARIABLE:	GIBBONS ET AL. COHORT STUDY	OLESEN ET AL. COHORT STUDY	OLESEN ET AL. CASE-CROSSOVER STUDY	PATORNO ET AL. COHORT STUDY	VANCOTT ET AL. NESTED MATCHED CASE-CONTROL STUDY
Measure and control for prior suicidal behavior	Yes, excluded attempt in the year prior to index diagnosis	No	No	Yes, excluded attempt in the 6 months prior to study entry	Yes, time period not specified
Control for history of mood and psychiatric disorders	Yes	Yes	Yes	Yes	Yes
Control for other factors influencing suicidality and use/selection of AEDs	Yes, study was restricted to bipolar disorder; demographic and medical factors	Yes, demographic and medical factors	Yes, demographic and medical factors; cases were their own controls	Yes, large list of demographic and medical factors	Yes, demographic and medical factors
Referent drug for comparison to AED	No drug, including lithium	CBZ	No drug	Primary = TPM Secondary = CBZ	GBP
Standardized approach to assessment of suicidal ideation or attempt	No	NA, only considered completed suicide	NA, only considered completed suicide	No	No
Considered full range of suicidality from ideation to completed suicide	No, suicide attempt only	No, completed only	No, completed only	No, attempt and completed only; plus violent deaths	No, ideation and attempt only

References: Gibbons et al. (27); Olesen et al. (28); Patorno et al. (29); VanCott et al. (30).
Abbreviations: CBZ, carbamazepine; TPM, topiramate; GBP, gabapentin.

TABLE 2. *Comparison of Findings for Individual Drugs as Reported in Four Studies, Compared to the FDA Analysis*

DRUG:	GIBBONS ET AL. RELATIVE TO NO DRUG* SA	OLESEN ET AL. COHORT STUDY: RELATIVE TO CBZ† CS	OLESEN ET AL. CASE CROSSOVER STUDY: RELATIVE TO NO DRUG CS	PATORNO ET AL. RELATIVE TO TPM‡ SA & CS	PATORNO ET AL. RELATIVE TO CBZ‡ SA & CS	VANCOTT ET AL. RELATIVE TO GBP§ SI & SA	FDA ANALYSIS RELATIVE TO PLACEBO OR OTHER AED SI, SA, & CS
CBZ	**2.37** **1.12–4.61**	1.0 Referent	0.48 0.21–1.12	1.08 0.56–2.08	1.0 Referent	1.2 0.3–5.5	0.65 0.08–4.42
CZP	-	**2.72** **1.77–4.17**	**2.01** **1.25–3.25**				-
CLB	-		0.59 0.05–7.43				-
GBP	1.16 0.66–2.05	1.27 0.66–2.44	2.20 0.83–5,83	**1.99** **1.45–2.73**	1.45 0.92–2.29	1.0 Referent	1.57 0.12–47.66
LTG	0.85 0.62–1.16	**2.09** **1.25–3.50**	**3.15** **1.35–7.34**	1.31 0.96–1.78	0.97 0.59–1.61	**10.2** **1.1–97.0**	**2.08** **1.03–4.40**
LVT	-	**5.91** **1.46–23.91**	-	0.62 0.28–1.37	1.10 0.47–2.58		2.75 0.62–19.36
OXC	0.98 0.62–1.56	1.69 0.81–3.56	0.84 0.30–2.32	**1.49** **1.01–2.20**	1.41 0.90–2.21	-	1.91 0.15–56.33
PB	-	**3.71** **2.30–5.99**	**1.96** **1.02–3.75**	1.64 0.37–7.33	1.12 0.45–2.75	0.8 0.2–2.6	-
PHT	-	2.16 0.30–15.46	0.37 0.03–4.44	1.44 0.41–5.10	**2.62** **1.03–6.70**	1.0 0.2–4.9	-
PGB	-		-	0.88 0.31–2.54	0.63 0.15–2.65	-	1.88 0.41–13.58
PMD	-	3.12 0.43–22.70	-	1.02 0.21–5.05	0.98 0.20–4.88	//	-
TGB	-		-	**1.98** **1.15–3.41**	1.23 0.72–2.09	-	∞ 0.20-∞
TPM	**1.87** **1.22–2.87**	2.11 0.67–6.67	2.72 0.23–32.78	1.0 Referent	0.80 0.48–1.34	-	**2.53** **1.21–5.85**
VPA	-	**2.40** **1.42–4.05**	**2.08** **1.04–4.16**	0.84 0.35–1.99	1.02 0.63–1.65	**2.3** **1.0–5.3**	0.72 0.29–1.84
ZNM	-		-	3.73 0.77–17.96	0.97 0.40–2.32	-	2.52 0.26–67.94
FB	-	-	-	-	-	-	ND
Any AED	0.88 0.72–1.08	-	-	-	-	-	**1.80** **1.24–2.66**

References: Gibbons et al. (27); Olesen et al. (28); Patorno et al. (29); VanCott et al. (30); FDA analysis (18).

*Adjusted for concomitant AEDs other than the 11 identified in the FDA report (18), antidepressants, antipsychotics, previous suicide attempts in the year before diagnosis of bipolar disorder, age, sex, and year.

†Adjusted for age, sex, socioeconomic status, Charlson score, civil status, diagnosis of epilepsy or a psychiatric disorder from 1978 to study inclusion, concomitant medication, and claimed prescription of opiate analgesics ≤180 days prior to study inclusion.

‡For Patorno et al. (29), the results of the propensity-matched analysis are shown.

§Adjusted for depression, anxiety, and posttraumatic stress disorder.

//Combined with Phenobarbital.

The numbers in bold face highlight the statistically significant associations.

Abbreviations: SA, suicide attempt; CS, completed suicide; SI, suicidal ideation; ND, no suicidality data observed; CBZ, carbamazepine; CZP, clonazepam; CLB, clobazam; GBP, gabapentin; LTG, lamotrigine; LVT, levetiracetam; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; PGB, pregabalin; PMD, primidone; TGB, tiagabine; TPM, topiramate; VPA, valproic acid; ZNM, zonisamide; FB, felbamate.

PharMetrics medical claims database to study the relationship between AEDs, lithium, and suicide attempt in 47,918 people with a first diagnosis of bipolar disorder and at least 1 year of follow up after diagnosis. Two periods were studied after the diagnosis of bipolar disorder: a pretreatment period and a posttreatment period. Pretreatment was defined as the time from bipolar disorder diagnosis to initiation of the first drug. The first drug was then used to label the pretreatment

period. For example, a person who was diagnosed with bipolar disorder but not prescribed drug therapy until 5 months later, when they were prescribed levetiracetam, would have a 5-month prelevetiracetam–treatment period, labeled by levetiracetam. There was no pretreatment period for people who were prescribed an AED or lithium on the day of diagnosis. Posttreatment was defined as the period from initiation of treatment after bipolar diagnosis to the end of the study. If a person was never prescribed an AED, there was no posttreatment period.

Overall, there were 843 suicide attempts among people on AEDs or lithium, people not taking AEDs or lithium, and people who were not medicated. All analyses compared treatment to no treatment based upon the drug prescribed in the posttreatment period. Suicide attempt during the pretreatment period and posttreatment period were separately analyzed, and they were compared to one another in Poisson regression models. A propensity-matched analysis, in which each patient was matched to another patient based upon her or his overall risk profile, was also presented. All analyses adjusted for suicide attempt in the year before bipolar disorder diagnosis, AEDs other than the 11 evaluated by the FDA (18), antidepressants, antipsychotics, age, sex, and calendar year. A strength of this study is the control for suicide attempt in the year preceding bipolar disorder diagnosis, as past suicide attempt was associated with a 12-fold increased risk for suicide attempt after diagnosis (R. Gibbons, pers. comm.).

Compared to no treatment, suicide attempts were significantly increased in the posttreatment period for topiramate (event rate ratio [ERR] = 1.87) and carbamazepine (ERR = 2.37). In the pretreatment period, suicide attempts were significantly increased for gabapentin (ERR = 6.11), valproic acid (ERR = 7.27), lamotrigine (ERR = 2.49), oxcarbazepine (ERR = 10.78), and topiramate (ERR = 3.96). Lithium was associated with an increased risk for suicide attempt in both periods. Comparisons of the risk for suicide attempt in the posttreatment versus the pretreatment period revealed that all AEDs were protective for posttreatment suicide attempt and was statistically significant for all agents except topiramate and carbamazepine.

Olesen et al.

Olesen et al. studied the relationship between AEDs and completed suicide in Danish population-based records-linkage databases (28). Two types of studies were conducted: a case-crossover study and a historical cohort study.

The case-crossover study included 6,780 cases with completed suicide, and there was no separate group of controls without suicide. Instead, each completed suicide case served as its own control, with the case period being the 30 days before the completed suicide and the two control periods being 60–90 days and 90–120 days before the suicide. This study design is akin to individually matching a person's case period to her or his own control period. AED exposure in the case period was compared to that in the control period. The design is problematic for several reasons, the most important of which is that control periods can contain episodes of suicidal ideation and suicide attempt. Thus, the control periods are contaminated by a less severe form of the case period to an unknown degree. Because prior suicidality is known to increase the risk for completed suicide (case period), irrespective of AED use, the design less informative than other designs about the effect of AEDs on the risk for completed suicide since prior suicidality during the control period is not adjusted for in the analysis (31,32). Clonazepam (odds ratio [OR] = 2.01), valproic acid (OR = 2.08), lamotrigine (OR = 3.15), and phenobarbital (OR = 1.96) were each associated with an increased risk for completed suicide. However, associations between completed suicide and the AEDs in this study could be completely explained by prior suicidality during the control period.

The Danish historical cohort study is based on a sounder study design than the case-crossover study. It followed 169,725 patients who were prescribed a new AED between 1997 and 2007 but had not been treated with an AED in 1996. Subjects were followed though the records-linkage system either until they experienced a completed suicide, the last day of 2006, or the date of death because of other causes. Again, no adjustment was made for a suicide attempt prior to entering the cohort and suicide attempts during follow-up were not addressed by adjustment or by censoring. The Cox model was adjusted for several confounders: age, gender, socioeconomic status, Charlson score, psychiatric disorders, diagnosis of epilepsy, and civil status. The authors found that clonazepam (hazards ratio [HR] = 2.72), valproic acid (HR = 2.40), lamotrigine (HR = 2.09), phenobarbital (HR = 3.71), and levetiracetam (HR = 5.91) were associated with a statistically significant increased risk for completed suicide compared to carbamazepine monotherapy.

Patorno et al.

Patorno et al. published a study of AEDs and suicide attempt, completed suicide, and violent injury using an insurance claims database (29). The study was based upon 297,620 AED-treatment episodes, 801 suicide attempts, 26 completed suicides, and 41 violent deaths (a total of 868 suicidal events).

The authors used topiramate as the primary referent against which each of the other AEDs was compared and then in a separate analysis used carbamazepine as the referent. An observation period began when an AED was first prescribed. Patients could contribute multiple observation periods to the study, provided there was a period of at least 6 months between

stopping one AED and starting another. Anyone with a known suicidal event during the 6 months before the beginning of the study time period (July, 2001) was excluded. Patients were censored from further analysis once they contributed one suicidal event. Two types of statistical approaches were used for analysis: 1) a proportional hazards multiple regression analysis that allows for statistical adjustment of known or potential confounders (e.g., age, gender, psychiatric diagnoses, or other medical conditions) in the 6 months before study entry and 2) a propensity score matched analysis in which each patient initiating a comparison drug is matched to another patient (based upon their overall risk profiles) initiating the referent drug. The latter approach likely provides tighter control for potential confounders.

The authors reported that, compared to topiramate, several AEDs were associated with a statistically significant increased risk, as indicated by the HR for suicide attempt or completed suicide (gabapentin HR = 1.42; lamotrigine HR = 1.84; oxcarbazepine HR = 2.07; tiagabine HR = 2.41; valproic acid HR = 1.65) after adjustment for all measured potential confounders in the proportional hazards analysis.

Careful comparison of the different proportional hazards models and the propensity score adjusted models, with topiramate and carbamazepine as referent drugs, is informative, although the proportional hazards model was not performed for carbamazepine. The effect estimates and the conclusions one can draw from these estimates are very sensitive to the type of analysis performed and the referent used, as illustrated in Table 3. For example, relative to topiramate, lamotrigine has a substantial and significant association with suicide in the crude analysis (HR = 3.90). This effect drops slightly after adjustment for sex and age (HR = 3.58) and is halved by adjustment for the available measured confounders (HR = 1.84). Once very tight control is made, however, through propensity matching, the relative difference between the two drugs drops even further and is no longer statistically significant (HR = 1.31). If lamotrigine is compared to carbamazepine, there is virtually no association; in fact, the point estimate is slightly below the null effect value of 1.00 (HR = 0.97).

VanCott et al.

The fourth study utilized data from the Veterans Administration and Medicare databases and focused specifically on veterans 66 years and older (30). The investigators identified all individuals who had received a new prescription for an AED but had not had any AED prescriptions in the previous year. They then created a matched case-control study in which cases (N = 64) with suicidal ideation or suicide attempt were matched to 12 controls (N = 768) who had not had any suicidal ideation based upon a history of these suicidal behaviors prior to prescription of the new AED, the diagnosis of epilepsy, and the year in which the AED was prescribed. AEDs studied included gabapentin (which was used as the referent drug and was the

TABLE 3. *Hazard Ratios and Risk Ratios for Each Drug Compared to Referent, as Found in Different Types of Analyses*

	TPM = REFERENT				CBZ = REFERENT
DRUG:	CRUDE HR*	SEX AND AGE ADJUSTED HR*	FULLY ADJUSTED HR*	PROPENSITY-MATCHED RR†	PROPENSITY-MATCHED RR‡
CBZ	1.22	1.38	1.24	1.08	-
GBP	0.95	1.48	1.42§	1.99	1.45
LTG	3.90	3.58	1.84§	1.31	0.97
LVT	1.34	1.57	1.63	0.62	1.10
OXC	4.60	3.88	2.07§	1.49	1.41
PB	1.24	1.54	0.99	1.64	1.12
PHT	0.94	1.23	1.25	1.44	2.62
PGB	0.63	1.30	1.18	0.88	0.63
PMD	0.51	1.08	1.15	1.02	0.98
TGB	3.88	4.38	2.41§	1.98	1.23
TPM	-	-	-	-	0.80
VPA	3.33	3.11	1.65§	0.84	1.02
ZNM	1.09	1.16	1.25	3.73	0.97

*From TABLE 4 in Patorno et al. (29).

† RR, relative risk; from e-table 6 (results for "as treated within 180 days") in Patorno et al. (29).

‡RR, relative risk; from e-table 9 (results for "as treated within 180 days") in Patorno et al. (29).

§Interpreted by Patorno et al. (29) as possibly posing an increased risk for suicidality.

Abbreviations: CBZ, carbamazepine; GBP, gabapentin; LTG, lamotrigine; LVT, levetiracetam; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; PGB, pregabalin; PMD, primidone; TGB, tiagabine; TPM, topiramate; VPA, valproic acid; ZNM, zonisamide.

most frequently prescribed; $N = 639$), carbamazepine ($N = 24$), phenobarbital (55), phenytoin ($N = 58$), valproic acid ($N = 49$), and lamotrigine and levetiracetam combined ($N = 7$). In a multiple conditional logistic regression analysis, psychiatric history (other than suicidality) was associated with an OR of 4.2, use of valproic acid with an OR of 2.3, and use of either lamotrigine or levetiracetam with an OR of 10.2, and each were reported as statistically significant, independent correlates of suicidal behavior. Relative to gabapentin, phenytoin (OR = 1.0), phenobarbital (OR = 0.8), and carbamazepine (OR = 1.2) were not associated with suicidal behaviors.

The identification of prior suicidal behavior by matching cases to controls as well as the adjustment for other mood and anxiety disorders is strengths of this study. A weakness is the inclusion of suicidal ideation, since suicidal ideation is unlikely to have been routinely recorded in Veterans Administration and Medicare databases. Of the four studies, however, this had the smallest number of suicidal behavior cases and the results for levetiracetam–lamotrigine (only seven cases and controls exposed in total) is hard to interpret. Nonetheless, the results at least provide one more piece of information about risks associated with the older AEDs. The protective effect of phenobarbital (OR = 0.8) was surprising, as this AED is known for its high risk of depressive episodes and suicidal ideation (33).

Comparison of the Four Studies

As mentioned, comparisons of the methods employed in the four studies are provided in Table 1, and the considerations of the findings for specific drugs are in Table 2. As can be seen, each study has selected strengths and weaknesses. Each study used a defined referent for all comparisons—sometimes an AED and sometimes no drug. All studies attempted to control for potential confounders, although to differing degrees. Three of the studies measured the single most important determinant of suicidality, past suicidality: 1) Gibbons et al. adjust for past suicide attempt in the year before bipolar disorder diagnosis (27), 2) Patorno et al. exclude individuals with a suicide attempt in the 6 months prior to initiating an AED (29), and 3) VanCott et al. matched this factor over an unspecified time period (30). Each investigation spans a relatively short time frame, considering that the risk for recurrent suicide attempt and for later completed suicide persists for decades (31,32). Because past suicide attempt is a very strong risk factor for recurrent suicide attempt and for completed suicide, far stronger than the risk for suicide attempt associated with AEDs, failure to adequately adjust for this factor may result in spurious associations between AEDs and suicidality.

The potential for bias is great in these studies and confounding by indication is of particular concern. Whether suicide attempt or completed suicide is the end point, suicidality is related both to the indications for AED treatment (e.g., psychiatric disorders, epilepsy, migraine) and to the selection of specific AEDs. Although confounding by indication is present in all of the studies, it is best illustrated in Gibbons et al. (27), in which compared to people who never received AED treatment, the pretreatment risk for suicide is substantially elevated for individuals taking AEDs compared to the posttreatment risk; the same is seen for lithium. This finding suggests that pretreatment suicide attempt is a marker of an increased severity in bipolar disorder and an indication for prescription with an AED. Failure to adjust completely for treatment indications can produce the kind of variability in results across studies that is highlighted in Table 2. Diagnostic suspicion bias is also a concern, because the studies were all record-based and without a standardized assessment of suicidal behaviors. A concern, therefore, is that monitoring influenced by the focus of specific types of physicians (e.g., psychiatrists vs migraine specialists) or according to the underlying disorders of the patients (e.g., psychiatric disorders vs migraine) led to different levels of patient monitoring and an increased or decrease in likelihood of identification of subsequent suicidal events in the diagnostic codes. These and related concerns are the types of considerations that raise doubts about the validity of results from the four studies reviewed here and the conclusions that can be drawn from them.

None of the four studies makes adjustments for multiple comparisons and some of the associations would no longer be statistically significant with such corrections. Most fragile are those drugs with the lower limit of the confidence interval very close to 1.0 (see Table 2), including phenobarbital and valproic acid in Olesen et al. (28), oxcarbazepine relative to topirimate in Patorno et al. (29), phenytoin relative to carbamazepine in Patorno et al., and valproic acid in VanCott et al. (30). These are additional reasons to be cautious about any conclusions drawn from the data.

Within a single study, the data from Patorno et al. demonstrate just how hard it can be to analyze suicidality after AED use in a nonrandomized setting (29). Table 3 illustrates the diversity of results that can occur when analyses are performed somewhat differently and control for an increasing number of factors. Fortunately, the authors published the range of results derived from the data. Each analysis is a reasonable approach to addressing potential confounding, though none adjusts for prior suicide attempt, and each provides a view through a particular lens, each lens introducing its own distortion. The illusive truth is not easily captured or recognized.

This dilemma is further demonstrated when comparisons are made across the four studies for the same drugs. In the Gibbons et al. (27) posttreatment analysis, topiramate and carbamazepine are the only drugs associated with an increased risk compared to no treatment. Yet, these are the very AEDs

used by Patorno et al. (29) as referent drugs. In examining the analysis in which topiramate is the comparator, tiagabine and gabapentin show increased risk, which likely reflects the impact of unmeasured and uncontrolled confounding. In the FDA analysis that gave rise to these four investigations (see Table 2), only lamotrigine and topiramate are significantly associated with suicidality (18), which is not consistently the outcome in the observational studies. In fact, there is little that is consistent among the studies or that can be easily reconciled with the hypothesis that AEDs, in general, or specific ones, in particular, increase the risk of suicidality.

Are the Data from Any of These Studies Concordant with Clinical Experience?

Of the four studies reviewed here, the findings by Gibbons et al. (27) are probably closest to the published clinical data, but all the studies show lack of concordance. First, the pretreatment data in the Gibbons et al. study are consistent with the known high suicidality rates in bipolar disease, which has been associated with lifetime estimates of suicide attempts that are close to 30% (7). Second, while Gibbons et al. observed a protective effect of valproic acid, lamotrigine, and oxcarbazepine for suicide attempt, lamotrigine and oxcarbazepine have not been tested for this protective effect in randomized clinical trials and valproic acid has only been tested against lithium. Third, the lack of a statistically significant difference between pre- and posttreatment suicidal attempts among patients taking topiramate is surprising, given its high incidence of negative psychotropic properties.

The study by Patorno and colleagues suggests that topiramate was the AED with the lowest suicidal risk (29). This was the most surprising result in any of the four studies, as topiramate is among the AEDs with the more frequent psychiatric adverse events, including depression and anxiety symptoms, which can facilitate the occurrence of suicidal phenomena.

Concluding Remarks

Eighteen months after the publication of the FDA meta-analysis, clinicians have become more aware of the increased suicidal risk of patients with epilepsy (18). That is the good news! However, the same questions and controversial issues raised by the FDA meta-analysis remain unanswered today. The contradictory data generated by the four large studies reviewed in this article illustrate the inherent difficulties in using retrospective studies to analyze a problem like suicide, for which putative pathogenic mechanisms are multifactorial, be it in people with epilepsy or mood disorders. Clearly, the only study design that can establish whether AEDs have an impact on suicidality is the *prospective*, randomized, double-blind, controlled trial, in which all the relevant variables are gathered in a systematic manner and the trials are conducted separately for each specific neurologic or psychiatric condition. Short of such studies, no objective answer will be obtained—no matter how sophisticated the statistical methods.

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