

Relationship Between Antiepileptic Drugs and Suicide Attempts in Patients With Bipolar Disorder

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Context: On January 31, 2008, the Food and Drug Administration issued an alert regarding increased risk of suicidal thoughts and behavior related to use of antiepileptic drugs (AEDs). On July 10, 2008, a Food and Drug Administration scientific advisory committee voted that, yes, there was a significant positive association between AEDs and suicidality but voted against placing a black box warning on AEDs for suicidality.

Objective: To determine if AEDs increase the risk of suicide attempt in patients with bipolar disorder.

Design: A pharmacoepidemiologic study in which suicide attempt rates were compared before and after treatment and with a medication-free control group. Analyses were restricted to AED and lithium monotherapy.

Setting: We used the PharMetrics medical claims database to study the relationship between the 11 AEDs identified in the FDA alert, and lithium, to suicide attempts.

Main Outcome Measure: Suicide attempts.

Patients: A cohort of 47 918 patients with bipolar dis-

order with a minimum 1-year window of information before and after the index date of their illness.

Results: Overall, there was no significant difference in suicide attempt rates for patients treated with an AED (13 per 1000 person-years [PY]) vs patients not treated with an AED or lithium (13 per 1000 PY). In AED-treated subjects, the rate of suicide attempts was significantly higher before treatment (72 per 1000 PY) than after (13 per 1000 PY). In patients receiving no concomitant treatment with an antidepressant, other AED, or antipsychotic, AEDs were significantly protective relative to no pharmacologic treatment (3 per 1000 vs 15 per 1000 PY).

Conclusions: Despite Food and Drug Administration reports regarding increased risk of suicidality associated with AED treatment, the current study reveals that, as a class, AEDs do not increase risk of suicide attempts in patients with bipolar disorder relative to patients not treated with an AED or lithium. Use of AEDs reduces suicide attempt rates both relative to patients not receiving any psychotropic medication and relative to their pretreatment levels.

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ANTICONVULSANT MEDICATIONS are life saving in the treatment of seizure disorders and are also extensively used for other indications such as mood disorders and trigeminal neuralgia. In March 2005, the Food and Drug Administration (FDA) sent letters to sponsors of 11 antiepileptic drugs (AEDs) requesting the submission of suicidality data from randomized clinical trials. The data consisted of suicide-related adverse event reports and a search for suicide-related terms in electronic databases related to the studies. The 11 AEDs included gabapentin, divalproex, felbamate, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, zonisamide, and carbamazepine. The FDA¹ conducted a meta-analysis of 199 placebo-controlled trials that included 43 892 patients (27 863 in drug-treatment groups and 16 029 in placebo). A total of 0.43% of the patients in drug treatment groups reported suicidal behavior or ideation vs

0.22% of the patients in placebo groups. Compared with placebo controls, 2.1 per 1000 more treated patients (95% confidence interval [CI], 0.7-4.2) reported suicidal behavior or ideation. On January 31, 2008, the FDA issued an alert to health care providers warning of increased risk of suicidal thoughts and behavior related to AEDs.² On July 10, 2008, the FDA's scientific advisory committee voted that there was a significant association between AEDs and suicidality but voted against a black box warning.

Previous pharmacoepidemiologic studies of AEDs and suicide in bipolar patients have been conducted.^{3,4} One study³ compared suicide completion and attempt rates between lithium, gabapentin, divalproex, and carbamazepine in a cohort of 12 662 bipolar patients from an Oregon Medicaid medical claims database. There were 11 suicides and 79 attempts. Relative to lithium, divalproex had higher suicide attempt (SA) rates and gabapentin had higher rates of suicide completion. The authors concluded

that lithium may have protective effects; however, it remained unclear whether lithium protects these patients against suicide completion. They also note that the difference between lithium and gabapentin related to suicide rates could be owing to confounding by indication, where gabapentin users may also have chronic pain and be at even higher suicide risk. The study did not control for previous SAs or previous treatment with lithium. It may be that more severely ill patients who did not respond to lithium were then prescribed gabapentin, and it is this lack of treatment response that is related to increased suicide incidence. The study was limited to only 11 suicides, and has not been replicated.

The second study⁴ involved 20 638 patients with bipolar disorder from 2 large integrated health plans from California and Washington. Suicide attempt rates were 31.3 per 1000 person-years (PY) for divalproex vs 10.8 per 1000 PY for lithium, a significant difference following adjustment for age, sex, comorbid medical and psychiatric conditions, and concomitant use of other psychotropic drugs. Completed suicide rates were also higher for divalproex vs lithium (1.7 per 1000 vs 0.7 per 1000 PY). Again, there was no adjustment for previous SAs or comparison with patients who were not treated with either lithium or an AED.

Completed suicide and attempted suicide are major concerns for people with bipolar disorder.⁵⁻⁸ Without treatment, approximately 10 per 1000 individuals with bipolar disorder complete suicide annually, and about 40 per 1000 attempt suicide.⁵ These risks of completed suicide and SA are approximately 100-fold and 10-fold higher, respectively than for the general population.⁵ That makes this a population of interest in detecting the effect on suicide risk of AEDs compared with a no-treatment control group. Further, the FDA warning implicated all 11 AEDs, which is surprising given their often quite different modes of action. This article examines the association between AED treatment and risk of SA exclusively in a population of bipolar patients. Relative to previous studies, we examined a larger cohort of bipolar patients and a larger set of AEDs (ie, 11 AEDs and lithium) and considered monotherapy only, thereby reducing the confounding effect of treatment resistance from the analysis. We also adjusted for concomitant therapy (antidepressants, antipsychotics, and other anticonvulsants) and SAs in the year prior to diagnosis. Our 2 primary analyses compared SA rates between individuals who did or did not receive AED or lithium treatment as well as within individuals before and after initiation of treatment. Finally, we performed a series of sensitivity analyses to determine the extent to which our findings were dependent on the various assumptions underlying our primary analysis.

METHODS

DATA

Data for this study came from the PharMetrics Patient Centric Database, the largest national patient-centric database of longitudinal integrated health care claims data, commercially available from PharMetrics, Inc (Watertown, Massachusetts), under unrestricted license. These national data are not statistically

different from the 2000 US Census distributions of age, sex, and region. The data comprise medical, specialty, facility, and pharmacy paid claims from more than 85 managed care plans nationally, representing more than 47 million covered lives.

DEFINITION OF COHORT AND SA

Data were collected during fiscal years 2000 through 2006. All patients with an *International Classification of Diseases, Ninth Revision (ICD-9)* diagnosis of bipolar disorder (ICD-9 codes 296.0x, 296.1x, and 296.4x-296.8x) who were continuously enrolled in the same health care plan for at least 1 year before and after the index diagnosis date were included in the sample. A total of 47 918 patients met these criteria, and there were 1226 patients with at least 1 SA. The ICD-9 codes used to identify SAs were E950 through E959, where the subcategories are E950 through E952 (self-inflicted poisoning), E953 (self-inflicted injury by hanging), E954 (drowning), E955 (self-inflicted injury by firearms), E956 (self-inflicted injury by cutting), E957 (self-inflicted injury by jumping from high places), E958 (other/unspecified self-inflicted injury), and E959 (late effects of self-inflicted injury). Based on this definition, our discussion of SAs includes deliberate self harm.

TREATMENT AND COMPARATOR GROUPS

To help insulate our findings from bias, we restricted our attention to AED monotherapy, defined for the 1-year period following the index episode as taking only 1 of the 11 AEDs and not taking lithium. Concomitant antidepressant, other anticonvulsant, and antipsychotic medications were included as covariates. Lithium monotherapy was also examined. As comparator groups, we considered (1) patients who received none of the 11 AEDs or lithium following diagnosis and (2) patients who received no central nervous system (CNS) medication.

PRIMARY ANALYSIS

Primary analysis of these data was based on Poisson regression models using the number of patient exposure days as an offset. The method of generalized estimating equations was used for within-subject analyses, which compared SA rates before and after initiation of therapy. Poisson regression analysis was used for between-subject comparisons of no medication (ie, 11 AEDs and lithium) with pretreatment and posttreatment AED and lithium conditions. Comparing no AED/lithium treatment with the pretreatment period allows us to examine selection effects. The term *pretreatment* indicates treatment prior to the initiation of AED or lithium monotherapy from the time of diagnosis. To adjust for other potential confounders, all models included concomitant other anticonvulsants, antidepressants, antipsychotics, previous SAs (in the year prior to the index diagnosis), age, sex, and year (2000-2006) as covariates. Results were expressed as event rate ratios (ERR) and associated CIs. The ERR is a rate multiplier that reflects the increased rate associated with treatment vs no treatment. An ERR of 2.0 reflects a doubling of the rate, whereas an ERR of 0.5 reflects half the risk.

SENSITIVITY ANALYSES

A series of sensitivity analyses were performed to examine various aspects of our primary model specification on the results of our analyses. These sensitivity analyses included (1) monotherapy defined up to the first SA or 1 year (logistic regression), (2) same as (1) but restricted to patients with at least a 30-day supply of an AED, (3) same as (1) but excluding patients with SAs on the day of the index diagnosis.

Table 1. Suicide Attempt Rate per 1000 PY Before and After Treatment With an AED and Lithium vs No Treatment

Drug	Patients at Risk of SA, No.	SA Before Treatment		SA Rate Before Treatment per 1000 PY	SA After Treatment		SA Rate After Treatment per 1000 PY
		No.	PY		No.	PY	
Gabapentin	1229	13	213	61	13	1016	13
Divalproex	4581	40	412	97	38	4169	9
Felbamate	NA						
Lamotrigine	4412	24	613	39	50	3799	13
Levetiracetam	42	0	6	0	0	36	0
Oxcarbazepine	1463	30	164	183	20	1299	15
Pregabalin	85	0	29	0	0	56	0
Tiagabine	80	0	16	0	0	64	0
Topiramate	1063	11	184	60	24	879	27
Zonisamide	84	2	11	182	0	73	0
Carbamazepine	346	2	40	50	9	306	29
Any of 11 AEDs	13 385	122	1688	72	154	11 697	13
11 AEDs only	1910	9	204	44	5	1706	3
Lithium	2518	23	233	99	40	2285	18
No AED or lithium	25 432	334	25 432	13			
No medication	11 207	170	11 207	15			

Abbreviations: AED, antiepileptic drug; NA, not applicable; PY, person-years; SA, suicide attempt.

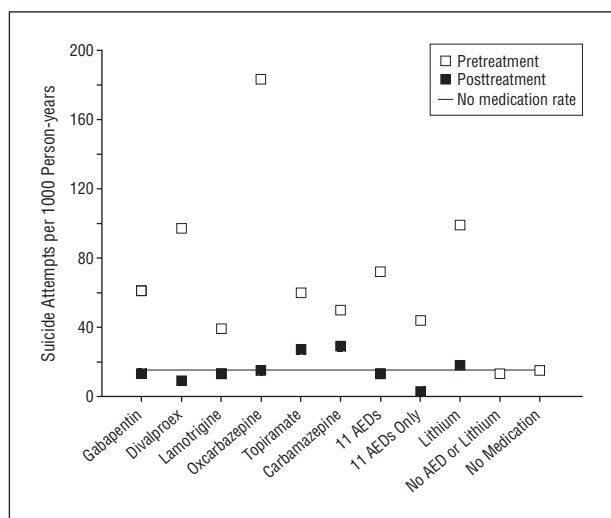


Figure 1. Suicide attempt rates before and after treatment by treatment type. AED indicates antiepileptic drug.

As a further sensitivity analysis (4) we used a person-time logistic regression model^{9,10} in which AED treatment was modeled as a time-varying covariate, and the hazard rate of SA was estimated on a month-by-month basis. Unlike the previous analyses in which exposure was considered constant from the time of treatment initiation through the 1-year follow-up, in this analysis, treatment was evaluated on a month-by-month basis. This analysis combines patients who did not take an AED with nonmedication months for patients who did take an AED and compares them with active treatment months. This analysis determines the effects of duration and pattern of exposure on our overall conclusions. This model also adjusted for month, which allowed the risk of SA to decrease (or increase) over time. An additional sensitivity analysis (5) was the same as (4) but was restricted to those highest-risk patients who had an SA in the year prior to the index episode.

The final sensitivity analysis (6) was conducted in an attempt to provide a causal inference. In this analysis we used propensity score matching¹¹ to obtain a 1:1 matched sample of patients who took AED monotherapy vs those who did not take

an AED or lithium in which potential confounders included the previously described covariates. For each pair (ie, AED vs no AED or lithium), the number of days after diagnosis for the treated patient was used to define the exposure period. A simple comparison of rates between the AED and non-AED groups (pre-exposure and postexposure) was then performed using generalized estimating equations. This analysis provides a causal inference to the extent that the propensity score matching adjusts for confounding between patients who were treated and those who were not, and the matching of the date of treatment initiation adjusts for the natural course of SAs over time (ie, they become less frequent as a function of time from the index episode¹²).

RESULTS

PRIMARY ANALYSIS

Table 1 presents the number of patients at risk, number of SAs, PY of exposure, and rate of SAs per 1000 PY of exposure before and after initiation of treatment during the year following the index diagnosis. These statistics are provided for each of the AEDs, lithium, the combination of all AEDs, no AEDs or lithium, and no CNS treatment at all. **Table 1** illustrates that a total of 13 385 patients received 1 of the 11 AEDs and 25 432 did not receive any of the 11 AEDs or lithium. Posttreatment SA rates for AEDs (13 per 1000 PY) and lithium (18 per 1000 PY) were comparable with no-treatment rates (13 per 1000 PY). Of the 25 432 patients who did not receive an AED or lithium, 11 207 (44%) also did not receive any other CNS medication. Their SA rate was 15 per 1000 PY. Felbamate, levetiracetam, pregabalin, tiagabine, and zonisamide had insufficient data for drug-level analysis. **Figure 1** presents a graphical summary of SA by treatment (before and after).

Following treatment, there was no overall significant difference in SA rates for patients treated with an AED (13 per 1000 PY) vs patients not treated with an AED or lithium (13 per 1000 PY; ERR, 0.88; 95% CI, 0.72-1.08;

Table 2. Comparison of Suicide Rates Before and After Treatment With an AED and Lithium vs No Treatment^a

Drug	Posttreatment vs No Treatment		Pretreatment vs No Treatment		Posttreatment vs Pretreatment	
	ERR (95% CI)	P Value	ERR (95% CI)	P Value	ERR (95% CI)	P Value
Gabapentin	1.16 (0.66-2.05)	.60	6.11 (3.46-10.79)	<.001	0.15 (0.05-0.47)	.001
Divalproex	0.72 (0.51-1.02)	.06	7.27 (5.16-10.25)	<.001	0.10 (0.05-0.19)	<.001
Lamotrigine	0.85 (0.62-1.16)	.31	2.49 (1.63-3.81)	<.001	0.33 (0.19-0.59)	<.001
Oxcarbazepine	0.98 (0.62-1.56)	.94	10.78 (7.31-15.86)	<.001	0.09 (0.04-0.24)	<.001
Topiramate	1.87 (1.22-2.87)	.004	3.96 (2.15-7.29)	<.001	0.52 (0.18-1.48)	.22
Carbamazepine	2.37 (1.21-4.61)	.01	3.21 (0.80-12.94)	.10	0.76 (0.10-6.01)	.80
Lithium	1.46 (1.04-2.03)	.03	7.19 (4.65-11.11)	<.001	0.23 (0.11-0.49)	<.001
Any AED	0.88 (0.72-1.08)	.22	4.88 (3.91-6.09)	<.001	0.19 (0.11-0.26)	<.001
AED only	0.19 (0.08-0.47)	<.001	2.85 (1.46-5.57)	.002	0.05 (0.02-0.18)	<.001

Abbreviations: AED, antiepileptic drug; CI, confidence interval; ERR, event rate ratio.

^aERR = 2.0 indicates doubling of the rate; ERR = 0.5, halving of the rate. These are adjusted for concomitant other AEDs (other than the 11 identified by the Food and Drug Administration), antidepressants, antipsychotics, previous suicide attempts (in the year prior to the index diagnosis), age, sex, and year (2000-2006).

$P = .22$). Similar results were seen for the individual AEDs, with the exception of topiramate (27 per 1000 PY; ERR, 1.87; 95% CI, 1.22-2.87; $P = .004$) and carbamazepine (29 per 1000 PY; ERR, 2.37; 95% CI, 1.21-4.61; $P = .01$), which had significantly greater posttreatment risk relative to no treatment (**Table 2**). A small but significant posttreatment increase for lithium vs no treatment was also found (ERR, 1.46; 95% CI, 1.04-2.03; $P = .03$). Overall, AEDs were associated with lower SA rates than lithium (13 per 1000 vs 18 per 1000 PY; ERR, 0.62; 95% CI, 0.44-0.89; $P = .008$); however, pretreatment SA rates were not significantly higher for patients treated with lithium (99 per 1000 PY) relative to AEDs (72 per 1000 PY; adjusted ERR, 0.80; 95% CI, 0.51-1.25; $P = .33$). While not statistically significant, the increased rate of SAs observed before treatment for lithium might account for the modestly higher posttreatment rate for lithium relative to AEDs.

The rate of SAs was significantly greater prior to any AED treatment (72 per 1000 PY) than after (13 per 1000 PY; ERR, 0.19; 95% CI, 0.11-0.26; $P < .001$). Similar reductions in SA rates were seen for the individual drugs and lithium, although the results for topiramate (60 per 1000 vs 27 per 1000 PY; ERR, 0.52; 95% CI, 0.18-1.48; $P = .22$) and carbamazepine (50 per 1000 vs 29 per 1000 PY; ERR, 0.76; 95% CI, 0.10-6.01; $P = .80$) were not statistically significant (Table 2). The pretreatment rate of SAs in patients who ultimately received AED treatment was significantly higher than the no-treatment SA rate (ERR, 4.88; 95% CI, 3.91-6.09; $P < .001$), suggesting that patients who received AED treatment were more severely impaired. A similar result was found for lithium (Table 2).

Suicide attempt rates for patients not treated with a CNS drug (15 per 1000 PY) were significantly higher (ERR, 0.19; 95% CI, 0.08-0.47; $P < .001$) than for patients treated with an AED only (3 per 1000 PY). In the absence of concomitant treatment, AEDs were associated with significantly decreased risk of SA relative to untreated patients, despite an almost 3-fold increased risk prior to treatment (44 per 1000 vs 15 per 1000 PY; ERR, 2.85; 95% CI, 1.46-5.57; $P = .002$), and exhibited significant reduction with treatment. The posttreatment adjusted SA rate was one-twentieth of the pretreatment rate (44 per 1000 vs 3 per 1000 PY; ERR, 0.05; 95% CI, 0.02-0.18; $P < .001$).

SENSITIVITY ANALYSES

The sensitivity analyses reported here are for all AEDs combined. Similar results were found for the individual AEDs (available from the authors), but they have less statistical power because of reduced sample size. All but the last sensitivity analysis were restricted to a single SA per individual. The first sensitivity analysis defined monotherapy prior to the first SA if present. The odds ratio (OR) for any AED vs no AED or lithium was (OR, 0.58; 95% CI, 0.48-0.71; $P < .001$; 12.6 per 1000 vs 15.3 per 1000 PY). The second sensitivity analysis only considered the AED to be present if the cumulative prescription(s) consisted of a supply of 30 days or more, and revealed similar results (OR, 0.58; 95% CI, 0.47-0.71; $P < .001$; 12.5 per 1000 vs 15.3 per 1000 PY). The third sensitivity analysis excluded SAs made on the index episode date and revealed no significant treatment-related differences (OR, 0.91; 95% CI, 0.73-1.12; $P = .37$).

The fourth sensitivity analysis was a person-time logistic regression model that related AED treatment on a monthly basis to the first SA. A significant decrease in SA rate associated with AED treatment (OR, 0.59; 95% CI, 0.47-0.75; $P < .001$) was found. **Figure 2** presents the estimated hazard functions (after diagnosis) for treated and untreated patients.

Overall, the SA rate decreases with time; however, the rates are lower in AED-treated patients throughout. Restricting the analysis to only patients ($n = 662$) who had an SA in the year prior to the index diagnosis revealed an even larger decrease in SA rate associated with treatment (OR, 0.35; 95% CI, 0.17-0.74; $P = .005$).

The final sensitivity analysis involved 1:1 propensity score matching of patients who did and did not take an AED and initial exposure date assignment for each pair based on the patient who took an AED. **Table 3** presents the covariate distributions for AED and no-AED groups before and after matching. Table 3 presents differences in means for age, proportions (all other variables), and standardized differences (mean or proportion difference divided by pooled standard deviation). As a rule of thumb, standardized differences of 10% or less

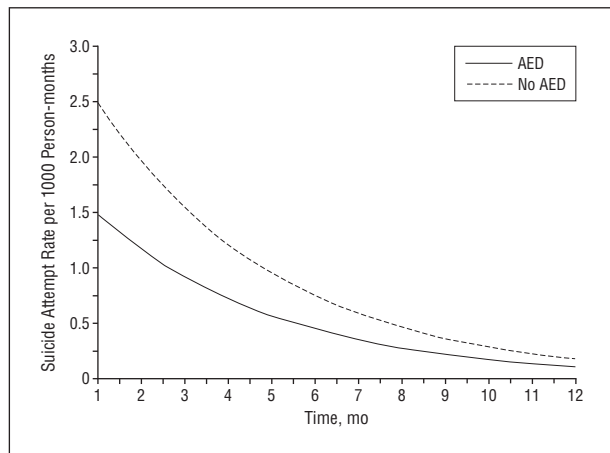


Figure 2. Hazard functions for suicide rates over time. Comparisons of patients treated with an antiepileptic drug (AED) vs patients not treated with an AED were adjusted for age, sex, concomitant treatment, previous suicide attempt, and year.

are considered well matched.¹³ Table 3 illustrates large imbalances prior to matching that disappear in the matched sample. Comparison of the AED and no-AED groups revealed that, prior to treatment, the rate of SAs was 70.52 per 1000 PY for treated and 38.07 per 1000 PY for untreated (OR, 1.85; 95% CI, 1.22-2.81; $P = .004$). Following treatment, the SA rate was 12.88 per 1000 PY for the treated and 10.46 per 1000 for untreated persons (OR, 1.23; CI, 0.89-1.71; $P = .22$). These results reveal that, even after matching, the pretreatment SA rate is significantly elevated; however, following treatment there is no significant difference in SA rates between those who did and did not receive AED treatment.

COMMENT

Drawing causal inference from observational data is complicated in general, but even more complicated for the study of suicide. First, suicide and SAs are rare events, and their determinants are difficult to estimate precisely in all but the largest samples. Second, suicide is related to the indication for treatment (ie, a psychiatric disorder) and is therefore difficult to separate from the possible effects of treatment. Third, an SA can lead to identification of the psychiatric disorder, which can, in turn, lead to treatment. It is not uncommon to find patients who have an SA, diagnosis of depression or bipolar disorder, and initiation treatment all on the same day. While this SA is not the consequence of initiating treatment, it can inflate the rate of SAs observed prior to initiation of treatment or in patients who do not receive treatment. Fourth, the natural course of psychiatric illnesses exhibits a decrease in SAs over time from diagnosis. This can make it appear that the SA rate is higher prior to treatment initiation than after, giving the false appearance of a protective effect. Fifth, patients who receive treatment often have increased severity of illness and may therefore be at increased suicide risk to begin with.

This study reveals that AEDs do not increase the risk of SAs relative to patients not treated with an AED or lithium. Of the patients not receiving any concomitant

treatment, the SA rate in AED-treated patients was significantly lower than in untreated patients.

Our analysis also reveals that there is a selection effect, in that the pretreatment SA rate is 5 times higher than the rate in untreated patients. If pretreatment SA rates reflect the severity of illness, it is the more severely impaired patients who receive treatment with an AED or lithium. Nevertheless, the posttreatment SA rate is significantly reduced relative to their elevated pretreatment levels to the level found at or below patients not receiving treatment. This finding suggests a possible protective effect of AED treatment on suicidality. Similar findings for lithium¹⁴ and both lithium and AEDs¹⁵ have been reported.

Possible exceptions are topiramate and carbamazepine, which did not show significant reduction in SA rates with treatment and revealed posttreatment SA rates significantly higher than untreated levels. Nevertheless, even for these 2 AEDs, there was no evidence that they increased suicide rates.

Sensitivity analyses revealed that our findings were robust to duration of treatment, defined as duration of 30 days or more, or defined on a monthly basis. The later analysis reveals that, despite the systematic decreases in SA rates over time, there remains a statistically significant decrease in SA rates for patients treated with an AED. Similar results were found for multiple attempts or a single attempt per person. Similar results were observed when monotherapy was defined for the entire year following the index episode or just until the first SA. The exclusion of all SAs that occurred on the index episode date produced an OR of less than 1.0, but was no longer statistically significant. This finding suggests that some of the difference between patients treated with an AED and those not treated may be owing to the identification of bipolar disorder because of the SA. To further examine this possibility, we matched AED-treated and untreated patients in terms of potential confounders and compared pretreatment and posttreatment periods based on the treatment initiation day of the treated patient. Treated patients still had elevated pretreatment SA rates but no difference following treatment. Treatment with AED, therefore, appears to produce a larger decrease in SA rates because the patients who ultimately receive AED treatment have a higher rate of SAs prior to receiving treatment. The exception to this is the case of patients who received no CNS treatment at all vs those who only received an AED, for whom the post-AED treatment rate was significantly lower than the no-treatment rate (3 per 1000 vs 15 per 1000 PY). Finally, restricting attention to patients at highest risk for SA (ie, patients with an SA in the year prior to the index episode) revealed an even larger significant reduction in SA rate with AED treatment, suggesting that the benefits of AED treatment may be greatest for the highest-risk patients.

The question arises as to the source of the difference between the results reported here and the findings of the FDA meta-analysis of randomized clinical trials. There are several possibilities. First, the FDA analysis was based on adverse event reports of suicidal thoughts and behavior, whereas our analysis is based exclusively on SAs. Second, the FDA meta-analysis combined several indications including psychiatric, pain, and epilepsy. Note that

Table 3. Comparison of Patient Characteristic Distributions in Original and Propensity Score–Matched Samples

Characteristic	Original Data Set (n=38 817)			Matched Data Set (n=25 574)		
	Percentage			Percentage		
	No Treatment	AED	STD	No Treatment	AED	STD
Male	40.2	40.0	0.5	40.3	40.1	0.5
Previous suicide attempt	1.1	1.6	4.0	1.4	1.6	1.4
Anticonvulsant before index date	5.2	11.8	23.9	9.1	10.5	4.8
Anticonvulsant after index date	6.0	14.9	29.6	10.9	13.0	6.7
Antidepressant before index date	39.4	66.9	57.5	67.3	65.5	3.9
Antidepressant after index date	42.4	70.6	59.4	71.9	69.3	5.8
Antipsychotic before index date	13.1	23.6	27.4	21.4	22.5	2.6
Antipsychotic after index date	19.9	41.1	47.3	36.1	38.7	5.4
Mean (SD) age, y	35.4 (15.9)	34.6 (15.2)	4.9	34.6 (15.5)	34.7 (15.3)	0.7

Abbreviations: AED, antiepileptic drug; STD, standardized difference.

the FDA's subanalysis for psychiatric indications was not significant (OR, 1.51; CI, 0.95-2.45). Third, most of the suicidality events in the FDA analyses were observed for only 2 of the 11 AEDs, lamotrigine and topiramate. Sixty-one percent of the events were observed for these 2 drugs, and they were the only 2 drugs that showed significant association with suicidality risk (lamotrigine OR, 2.08; CI, 1.03-4.40; topiramate OR, 2.53; CI, 1.21-5.85). By contrast, the other 9 drugs showed no significant association with suicidality, either individually or combined (OR, 1.127; CI, 0.652-1.948; $P = .78$). The FDA meta-analysis could have been driven by lamotrigine and topiramate. Note that the increased overall risk of SA for lamotrigine may reflect the increased use and number of trials for psychiatric indications; however, this is not true for topiramate, and would not account for the increased ORs for these 2 drugs. Fourth, the results of the FDA analysis could be affected by 2 ascertainment biases. Patients treated with a drug will have more adverse effects than patients taking a placebo and, therefore, more opportunity to describe their suicidal thoughts.¹⁶ Suicide attempts by an overdose of study medication will result in contact with the health care system (eg, an emergency department), and therefore have a greater likelihood of being detected than an overdose while taking placebo.¹⁷

With respect to the previous report by Collins and McFarland,³ their study was restricted to lithium, divalproex, gabapentin, and carbamazepine. For these 4 drugs, they identified 79 SAs in 7017 PY, whereas we identified 100 attempts in 7776 PY, so the overall incidence rate for these 4 drugs was slightly higher in our study. In terms of SA rates, they found rates of 6, 19, 10, and 17 per 1000 PY for lithium, divalproex, gabapentin, and carbamazepine, respectively, whereas our posttreatment incidence rates were 18, 9, 13, and 29, respectively. Rates reported by Goodwin and colleagues⁴ were generally higher than those found by Collins and McFarland³ and somewhat closer to those in our study, with the exception of divalproex (11, 31, and 22 per 1000 PY for lithium, divalproex, and carbamazepine, respectively). Completed suicide rates for bipolar patients treated with lithium have been reported as 0.7 per 1000,¹⁸ 1.6 per 1000,⁴ and 1.9 per 1000¹⁴ PY.

The major differences between our study and the 2 previous studies are that (1) we were able to adjust for pretreatment SAs, (2) we considered AEDs and lithium monotherapy, whereas they designated patients in terms of their first treatment, (3) we included a no-treatment control group, and (4) we had pretreatment data that permitted a within-subject analysis.

Finally, our estimates of the untreated SA rate of 13 per 1000 PY for no treatment with any of the 11 AEDs or lithium and 15 per 1000 PY for no treatment with any AED, antidepressant, or antipsychotic medication is considerably less than the rate of 40 per 1000 PY reported by Baldessarini and colleagues.⁵ Note, however, that for the bipolar patients who go on to be treated with an AED, the rate is 72 SAs per 1000 PY and, for those who are ultimately treated with lithium, the SA rate is 99 per 1000 PY. As such, their reported rate of 40 per 1000 PY may be a reasonable estimate of the overall rate of SAs in untreated bipolar patients averaged for the entire range of severity of illness.

It should be noted that anticonvulsants, as a class, have not demonstrated thymoleptic efficacy in bipolar disorder. Some AEDs such as carbamazepine or divalproex exert mood regulation or have antidepressant effects, like lamotrigine; others, such as topiramate, gabapentin, or oxcarbazepine, apparently do not. Some AEDs have not been adequately evaluated, such as zonisamide, levetiracetam, and tiagabine. A comparison of anticonvulsants with known efficacy (including lithium) with those with no antimanic or antidepressant properties suggests that posttreatment SA rates are relatively similar. Carbamazepine and topiramate had the highest posttreatment SA rates, whereas divalproex had the lowest rate. Overall treatment efficacy, at least in randomized clinical trials, does not appear to adequately explain the differences in posttreatment SA rates observed in our study.

There are several limitations of our study. First, our results are based on medical claims data, and there is likely to be underreporting of SAs. Second, we do not have access to information on completed suicides in this population. Third, our analyses do not incorporate intensity of treatment. Fourth, patients were not randomized to treatment, and there may be other factors that play a signifi-

cant role in the process by which specific treatments are selected for patients. For example, drugs such as lamotrigine and divalproex are prescribed predominantly for bipolar disorder, and may therefore reflect higher suicide risk owing to confounding by indication. Fifth, diagnoses were obtained from electronic data systems and not from structured psychiatric interviews. Sixth, our analyses do not consider treatment adherence, which may play an important role in suicidal behavior. Seventh, while all patients in the cohort had bipolar disorder, there may have been concomitant diagnoses such as pain or epilepsy disorders for which the AED was actually prescribed. While this does not limit our ability to determine if there is an association between AED treatment and SAs, the comorbid diagnosis may further increase the suicidal risk in these patients.¹⁹ Finally, bipolar disorder is characterized by a large variety of symptom intensity and severity, which may further confound our ability to separate selection effects from the effects of AED treatment.

In summary, the present analysis provides no evidence that AEDs increase risk of SAs in patients with bipolar disorder. Most AEDs and lithium are associated with reduction in SA rates relative to pretreatment levels in patients who are ultimately prescribed these drugs. In patients treated with no other psychotropic medication, AEDs significantly reduced the SA rate to less than that of patients who received no psychopharmacological treatment, despite the fact that their pretreatment SA rate was almost 3 times higher than those who did not receive treatment. In the rest of the population, the SA rate in AED-treated patients is either equal to or significantly less than the rate for patients not treated with an AED, depending on the analysis and cohort examined.

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