

Anticonvulsant Medications and the Risk of Suicide, Attempted Suicide, or Violent Death

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ANTICONSULSANT MEDICATIONS are a heterogeneous pharmacologic class characterized by various chemical structures and postulated mechanisms of action. They represent the main therapeutic approach for patients with epilepsy, but labeled indications also include bipolar disorder, mania, neuralgia, migraine, and neuropathic pain.¹⁻³ Their off-label use is rapidly increasing as well.^{4,5} The wide range of indications and common use of anticonvulsants in patients with or without psychiatric comorbidities make their safety an issue of great relevance.

In 2008 the US Food and Drug Administration (FDA) published a meta-analysis including data from 199 placebo-controlled trials of 11 anticonvulsant drugs.⁶ The FDA found that patients taking anticonvulsant drugs had approximately twice the risk of suicidal behavior or ideation (0.43 per 100) compared with patients receiving placebo (0.22 per 100). Subsequently, the FDA required new labeling for all anticonvulsant medications, including a warning about the increased risk of suicidal thoughts and behavior.⁷⁻⁹ Although an increased risk in these outcomes was observed in the meta-analysis, its limited size and small number of events, largely representing cases of suicidal ideation only, pre-

Context In 2008, the US Food and Drug Administration mandated warning labeling for anticonvulsant medications regarding the increased risk of suicidal thoughts and behaviors. The decision was based on a meta-analysis not sufficiently large to investigate individual drugs.

Objective To evaluate the risk of suicidal acts and combined suicidal acts or violent death associated with individual anticonvulsants.

Design A cohort study of the risk of suicidal acts and combined suicidal acts or violent death in patients beginning use of anticonvulsant medications compared with patients initiating a reference anticonvulsant drug.

Setting and Patients Patients 15 years and older from the HealthCore Integrated Research Database (HIRD) who began taking an anticonvulsant between July 2001 and December 2006.

Main Outcome Measures Cox proportional hazards models and propensity score-matched analyses were used to evaluate risk of attempted or completed suicide and combined suicidal acts or violent death, controlling for psychiatric comorbidities and other risk factors, among individual anticonvulsants compared with topiramate and secondarily carbamazepine.

Results The study identified 26 completed suicides, 801 attempted suicides, and 41 violent deaths in 297 620 new episodes of treatment with an anticonvulsant (overall median follow-up, 60 days). The incidence of the composite outcomes of completed suicides, attempted suicides, and violent deaths for anticonvulsants used in at least 100 treatment episodes ranged from 6.2 per 1000 person-years for primidone to 34.3 per 1000 person-years for oxcarbazepine. The risk of suicidal acts was increased for gabapentin (hazard ratio [HR], 1.42; 95% confidence interval [CI], 1.11-1.80), lamotrigine (HR, 1.84; 95% CI, 1.43-2.37), oxcarbazepine (HR, 2.07; 95% CI, 1.52-2.80), tiagabine (HR, 2.41; 95% CI, 1.65-3.52), and valproate (HR, 1.65; 95% CI, 1.25-2.19), compared with topiramate. The analyses including violent death produced similar results. Gabapentin users had increased risk in subgroups of younger and older patients, patients with mood disorders, and patients with epilepsy or seizure when compared with carbamazepine.

Conclusion This exploratory analysis suggests that the use of gabapentin, lamotrigine, oxcarbazepine, and tiagabine, compared with the use of topiramate, may be associated with an increased risk of suicidal acts or violent deaths.

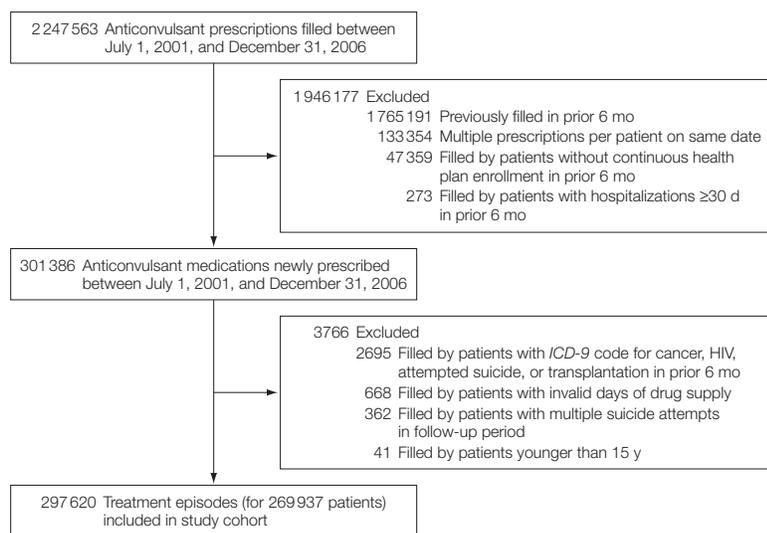
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vented definitive conclusions about the safety of individual agents. Furthermore, in many trials included in the meta-analysis, the anticonvulsant drugs were used as an adjunctive therapy, further complicating the assessment of their individual effect. Thus, the FDA meta-analysis could not provide patients or cli-

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Figure 1. Flowchart of Study Cohort of Treatment Episodes

ICD-9 indicates *International Classification of Diseases, Ninth Revision*; HIV, human immunodeficiency virus.

nicians with clear guidance on risk for specific agents or patient subgroups.¹⁰

The objective of this study was to evaluate the increased risk of attempted or completed suicide, and combined suicidal acts or violent death, associated with a range of individual anticonvulsant agents and within patient subgroups.

METHODS

We conducted a cohort study to compare the risk of attempted or completed suicide and combined suicidal acts or violent death in patients beginning to take anticonvulsant medications with the risk in patients beginning to take a reference anticonvulsant drug (primarily topiramate and secondarily carbamazepine). The analysis was restricted to new users of the study drugs to facilitate detection of events occurring shortly after initiation and to help define the relationship between duration of use and level of risk.¹¹

Data Source

Data included medical and pharmacy claims from the HealthCore Integrated Research Database (HIRD). The HIRD contains a broad spectrum of longitudinal claims data representing all filled prescriptions and clinical encounters from health plans in the southeastern,

mid-Atlantic, central, and western regions of the United States. For this study, data were available from January 1, 2004, for 14 US states (Delaware, Georgia, California, Virginia, New York, Nevada, Indiana, Kentucky, Missouri, Ohio, Wisconsin, Connecticut, Maine, and New Hampshire) with 3 states (Delaware, Georgia, and California) contributing data beginning January 1, 2001. The study cohort was followed up through December 31, 2006, the latest date for which data on the exact date and cause of death from the National Death Index (NDI) were available.

Study Population

All participants aged 15 years and older who began taking an anticonvulsant drug between July 2001 through December 2006, and who had 6 months of continuous health plan enrollment preceding the drug initiation date (index date), were eligible for the study cohort. Incident use required the absence of any anticonvulsant medication in the 6 months before the index date. Participants were excluded if they had received multiple anticonvulsant drugs on the index date and if, in the 6 months before the index date, they had recorded diagnoses for attempted suicide or medical conditions that could

have influenced the risk of suicidal acts, such as cancer, human immunodeficiency virus, or long hospitalization (length of stay >30 days) (FIGURE 1).

Personal identifiers were removed from the data set before the analysis to protect subject confidentiality. The study was approved by the institutional review board of Brigham and Women's Hospital and Quorum Review Inc.

Anticonvulsant Medications and Drug Exposure

The anticonvulsant medications considered included carbamazepine, ethosuximide, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, primidone, tiagabine, topiramate, valproate, and zonisamide. The heterogeneous utilization pattern of anticonvulsant medications makes the choice of a common reference drug particularly challenging. Topiramate was chosen as the primary reference drug because it was the second most commonly used agent in the study population and because it is used for a wide range of indications. However, despite its broad range of uses, topiramate is not commonly used as first-line therapeutic approach in epilepsy or seizure disorder. To investigate the risk of suicidal events in patients beginning to use anticonvulsants for epilepsy, we used carbamazepine, an anticonvulsant widely used for initial treatment of epilepsy, as a reference drug in a secondary analysis.

Based on the medication prescribed on the index date, each subject was identified as beginning to take a specific anticonvulsant agent. Follow-up began on the day following the initial fill date. Participants were followed up for 180 days, until drug discontinuation or switching, the occurrence of a study outcome, death for causes not included in the study outcome, end of continuous health plan enrollment, or the end of the observation period, whichever came first. Patients could have gaps of up to 30 days between prescription fill dates in the calculation of continuous therapy. In the case of drug discontinuation or switching, the ex-

posure risk window for each patient treatment episode extended until 30 days after the expiration of the supply of the last fill. Patients could contribute more than 1 treatment episode if they had a 6-month washout period without use of any study drug. In a secondary analysis mimicking an “intention-to-treat” approach, patients were followed up from the day following the first fill for 180 days without considering drug discontinuation or switching, carrying forward exposure to the first-used drug.

Outcomes

We identified suicide attempts through emergency department (ED) visits and hospitalizations with a diagnosis of suicide and self-inflicted injury (E950.x-958.x) coded using *International Classification of Diseases, Ninth Revision (ICD-9)*¹² and recorded in medical claims in the HIRD. The use of the ICD-9 coding system for the identification of suicide attempts has been found to have a positive predictive value of 86%.¹³ In addition, a validation study of injury-related deaths found that suicides are reliably documented on death certificates with specificity and sensitivity for the individual codes for intentional self-harm all greater than 90%.¹⁴ In the United States, ICD-9 E-codes are incompletely forwarded from hospitals to payers.¹⁵ To address this issue, for the identification of cases of attempted suicide, we also used an algorithm that combined specific ICD-9 codes for injuries with other diagnoses and that was shown to have a specificity of 98% and positive predictive value of 73% in a Nationwide Inpatient Sample.¹⁶ Participant data were censored after the first attempted suicide without considering other outcomes on subsequent treatment episodes.

After routine cross-checking of the HIRD with the US Social Security Administration Master Death Index to determine which members of the HIRD had died, we identified the exact date and cause of death for these patients from the NDI. Cases of completed suicide were identified through recorded ICD-10 codes for intentional self-harm (X60-

X84), while violent deaths were identified as S00-T78, V01-V99, W00-X59, and Y10-Y34.¹⁷ We chose to also investigate violent deaths because mortality due to injuries or accidents accounts for a proportion of suicides,^{14,18} reaching 87% among accidental deaths suspected as being suicidal.¹⁹

Potential Confounders and Other Variables

Patient characteristics were assessed during the 6 months preceding cohort entry, including the index date (the first fill). Demographic data (age and sex), calendar year, and comorbidities that could have been associated with a higher risk of attempted or completed suicide and violent death were investigated via ICD-9 codes and Current Procedural Terminology 4 codes (CPT-4)²⁰ and medication use via National Drug Codes. These comorbidities included psychiatric disorders, such as bipolar disorder, anxiety, psychotic disorders, substance abuse, delirium, dementia, and other psychiatric disorders; and neurological disorders, such as epilepsy and seizure disorders, neuropathy and neuropathic pain, migraine, head injury, Parkinson disease, multiple sclerosis, amyotrophic lateral sclerosis, and other neurological disorders. We also identified other comorbidities as potential confounders, including myocardial infarction, cerebrovascular disease, heart failure, diabetes mellitus, chronic lung disease, renal failure, and other severe chronic disorders, and health care utilization, including previous hospitalizations, physician visits, psychiatric hospitalizations, use of psychotropic medications, and total number of medications used.

Statistical Analysis

We then defined demographic characteristics and selected coexisting clinical conditions and health care utilization measures among new users of each anticonvulsant medication considered through cross-tabulations by drug exposure. For each medication exposure on the index date, the number of participants; number of treatment episodes; length of follow-up period; and num-

ber of events and incidence rates for attempted suicide, attempted or completed suicide, and any suicidal event or violent death were calculated until drug discontinuation or switching. The primary analysis was limited to 180 days of follow-up; in a secondary analysis we extended the follow-up period to 360 days. For the 180-day follow-up analysis, the population was followed up via 2 methods: until drug discontinuation or switching (primary as-treated analysis) and carrying forward the first drug exposure until day 180 (secondary cumulative analysis). The number of participants lost to 180 days of follow-up, excluding the number of participants who developed any suicidal event or violent death, was 245 398 in the primary as-treated analysis and 88 849 in the secondary cumulative analysis. These patients were censored at the time they were lost to follow-up.

To control for potential differences among new users of anticonvulsant medications, multivariate-adjusted Cox proportional hazards models were used as well as high-dimensional propensity score analysis.²¹ A 2-sided statistical significance level of .05 was applied.

We fitted unadjusted; age-, sex-, and calendar year-adjusted; and multivariate-adjusted (for all the variables previously mentioned) Cox proportional hazards models to evaluate all outcomes in 180 days among users of all anticonvulsant medications compared with new users of topiramate until discontinuation or switching of the study drug.

To improve covariate adjustment, we used high-dimensional propensity score estimation. Initiation of each anticonvulsant medication was modeled pairwise against topiramate initiation, the common reference group, and then propensity score-matched using the greedy matching algorithm,²² which has been shown to perform well in balancing 2 comparison groups.²³ Because pregabalin was not on the market before 2005, new users of pregabalin were propensity score-matched with topiramate beginning January 2005. Rate ratios (RRs) and rate differences (RDs) with 95% confidence intervals (CIs) for all outcomes

were calculated, and adjusted Kaplan-Meier curves were plotted among selected matched groups. Forest plots of the RRs for attempted or completed suicide were produced for subgroups defined by age (15-24 and 25-64 years), recorded diagnosis of mood disorders or its therapy (antidepressant medications or lithium), and recorded diagnosis of epilepsy or seizure disorders.

Adjustments for multiple comparisons were not considered. In this exploratory analysis, we limited analyses to estimation of effects and precision rather than any formal statistical testing.^{24,25} Statistical analyses were performed using SAS versions 9.1 and 9.2 (SAS Institute, Cary, North Carolina).

RESULTS

We identified 297 620 new treatment episodes of anticonvulsant medications (Figure 1), among which 57 853 were

represented by topiramate. The most frequently prescribed medications were gabapentin (48.0%), topiramate (19.4%), lamotrigine (7.5%), and valproate (6.2%). TABLE 1, TABLE 2, and eTable 1 (available at <http://www.jama.com>) show variations in patient characteristics among study drugs that are consistent with the wide spectrum of uses of anticonvulsant drugs. Patients beginning to take topiramate were more likely than patients beginning to take other anticonvulsant medications to be female, to have had a diagnosis of migraine or headache, to have had an ambulatory visit, and to have used antimigraine medications in the 6 months prior to drug initiation. New users of topiramate also had a lower proportion of epilepsy or seizure disorders and previous hospitalizations in the period preceding the drug initiation. The new users of other anticonvulsants were more likely to have had

diagnoses of epilepsy or seizure disorder (levetiracetam and phenytoin), neuropathic pain (carbamazepine, gabapentin, and pregabalin), depressive disorder, manic-depressive disorder, or anxiety (lamotrigine, oxcarbazepine, valproate, and tiagabine) and to have used antidepressant (lamotrigine and tiagabine), antipsychotic (lamotrigine and valproate), and analgesic medications (gabapentin, pregabalin, and tiagabine).

The overall mean (SD) follow-up for anticonvulsant medications was 91 (52) days and the median was 60 days (interquartile range, 60-125 days). The mean follow-up time for topiramate treatment was 97 days and the median was 60 days (TABLE 3). Patients beginning to take lamotrigine had the longest time receiving therapy, with mean and median follow-up periods of 109 and 98 days, respectively. Phenobarbital and pregabalin treatment episodes had the shortest

Table 1. Selected Patient Characteristics by Drug Exposure (New Treatment Episodes) for 7 of 13 Anticonvulsant Medications^a

| | No. (%) | | | | | | |
|--|---------------|---------------|----------------|---------------|---------------|---------------|---------------|
| | Topiramate | Carbamazepine | Gabapentin | Lamotrigine | Levetiracetam | Oxcarbazepine | Phenobarbital |
| Observations | 57 853 (19.4) | 9859 (3.3) | 142 865 (48.0) | 22 256 (7.5) | 3975 (1.3) | 8579 (2.9) | 2130 (0.7) |
| Demographics | | | | | | | |
| Female | 47 803 (82.6) | 5851 (59.3) | 86 846 (60.8) | 14 327 (64.4) | 2433 (61.2) | 5048 (58.8) | 1288 (60.5) |
| Age, mean (SD), y | 41 (13) | 46 (17) | 51 (14) | 38 (14) | 46 (17) | 37 (16) | 47 (16) |
| Median, y | 41 | 46 | 51 | 38 | 46 | 37 | 45 |
| Health services utilization | | | | | | | |
| No. of medications, mean (SD) | 8 (6) | 6 (6) | 9 (6) | 7 (6) | 7 (7) | 7 (6) | 7 (7) |
| Median, No. | 7 | 5 | 8 | 6 | 6 | 5 | 5 |
| Hospitalization | 4988 (8.6) | 1375 (13.9) | 22 764 (15.9) | 2746 (12.3) | 1160 (29.2) | 1542 (18.0) | 520 (24.4) |
| Ambulatory visits | 47 486 (82.1) | 6807 (69.0) | 110 696 (77.5) | 15 775 (70.9) | 3139 (79.0) | 6259 (73.0) | 1445 (67.8) |
| Hospitalization for any psychiatric disorder | 1984 (3.4) | 638 (6.5) | 6242 (4.4) | 1986 (8.9) | 397 (10.0) | 1007 (11.7) | 266 (12.5) |
| Neurological and psychiatric comorbidities | | | | | | | |
| Epilepsy | 618 (1.1) | 704 (7.1) | 386 (0.3) | 741 (3.3) | 773 (19.4) | 523 (6.1) | 123 (5.8) |
| Convulsions | 1041 (1.8) | 1174 (11.9) | 920 (0.6) | 926 (4.2) | 1289 (32.4) | 845 (9.8) | 215 (10.1) |
| Neuropathic pain | 1383 (2.4) | 1617 (16.4) | 23 202 (16.2) | 939 (4.2) | 362 (9.1) | 795 (9.3) | 116 (5.4) |
| Migraine | 21 293 (36.8) | 444 (4.5) | 6159 (4.3) | 990 (4.4) | 596 (15.0) | 398 (4.6) | 120 (5.6) |
| Depressive disorder | 9773 (16.9) | 1238 (12.6) | 15 374 (10.8) | 8963 (40.3) | 462 (11.6) | 2648 (30.9) | 265 (12.4) |
| Manic depressive disorder | 2426 (4.2) | 692 (7.0) | 2081 (1.5) | 6586 (29.6) | 62 (1.6) | 1843 (21.5) | 30 (1.4) |
| Psychosis | 516 (0.9) | 180 (1.8) | 961 (0.7) | 634 (2.8) | 121 (3.0) | 344 (4.0) | 30 (1.4) |
| Alcohol and drug abuse or dependence | 2195 (3.8) | 604 (6.1) | 6992 (4.9) | 1615 (7.3) | 279 (7.0) | 851 (9.9) | 363 (17.0) |
| Delirium | 183 (0.3) | 81 (0.8) | 594 (0.4) | 149 (0.7) | 75 (1.9) | 87 (1.0) | 26 (1.2) |
| Dementia | 239 (0.4) | 144 (1.5) | 1261 (0.9) | 135 (0.6) | 187 (4.7) | 122 (1.4) | 28 (1.3) |
| Other psychiatric disorders | 4709 (8.1) | 608 (6.2) | 6477 (4.5) | 3145 (14.1) | 306 (7.7) | 1385 (16.1) | 105 (4.9) |
| Use of other psychotropic medications | | | | | | | |
| Antidepressants | 29 963 (51.8) | 3211 (32.6) | 55 194 (38.6) | 15 266 (68.6) | 1592 (40.1) | 4803 (56.0) | 647 (30.4) |
| Lithium | 823 (1.4) | 242 (2.5) | 768 (0.5) | 2054 (9.2) | 34 (0.9) | 405 (4.7) | 11 (0.5) |
| Antipsychotics | 4725 (8.2) | 956 (9.7) | 6103 (4.3) | 5669 (25.5) | 273 (6.9) | 1806 (21.1) | 138 (6.5) |
| Analgesics | 28 319 (48.9) | 4145 (42.0) | 94 639 (66.2) | 6867 (30.9) | 1837 (46.2) | 3059 (35.7) | 924 (43.4) |

^aSix months prior to index date.

Table 2. Selected Patient Characteristics by Drug Exposure (New Treatment Episodes) for 6 of 13 Anticonvulsant Medications^a

| | No. (%) | | | | | |
|--|--------------|-------------|-------------|-------------|---------------|-------------|
| | Phenytoin | Pregabalin | Primidone | Tiagabine | Valproate | Zonisamide |
| Observations | 10 531 (3.5) | 9086 (3.1) | 3104 (1.0) | 5497 (1.9) | 18 295 (6.2) | 3528 (1.2) |
| Demographics | | | | | | |
| Female | 4640 (44.1) | 5419 (59.6) | 1567 (50.5) | 3320 (60.4) | 10 118 (55.3) | 2608 (73.9) |
| Age, mean (SD), y | 48 (18) | 56 (15) | 59 (16) | 44 (13) | 41 (18) | 43 (14) |
| Median, y | 48 | 55 | 60 | 44 | 39 | 43 |
| Health services utilization | | | | | | |
| No. of medications, mean (SD) | 6 (6) | 10 (7) | 8 (7) | 9 (7) | 7 (6) | 7 (7) |
| Median, No. | 4 | 9 | 7 | 8 | 6 | 6 |
| Hospitalization | 4657 (44.2) | 1311 (14.4) | 377 (12.1) | 734 (13.4) | 4045 (22.1) | 388 (11.0) |
| Ambulatory visits | 6230 (59.2) | 6135 (67.5) | 2477 (79.8) | 4526 (82.3) | 11 876 (64.9) | 2999 (85.0) |
| Hospitalization for any psychiatric disorder | 1597 (15.2) | 253 (2.8) | 89 (2.9) | 394 (7.2) | 2903 (15.9) | 128 (3.6) |
| Neurological and psychiatric comorbidities | | | | | | |
| Epilepsy | 1717 (16.3) | 34 (0.4) | 33 (1.1) | 27 (0.5) | 601 (3.3) | 164 (4.6) |
| Convulsions | 5141 (48.8) | 61 (0.7) | 62 (2.0) | 65 (1.2) | 1152 (6.3) | 206 (5.8) |
| Neuropathic pain | 169 (1.6) | 1154 (12.7) | 105 (3.4) | 312 (5.7) | 227 (1.2) | 174 (4.9) |
| Migraine | 360 (3.4) | 347 (3.8) | 70 (2.3) | 364 (6.6) | 2169 (11.9) | 884 (25.1) |
| Depressive disorder | 808 (7.7) | 751 (8.3) | 254 (8.2) | 1588 (28.9) | 5096 (27.9) | 567 (16.1) |
| Manic depressive disorder | 74 (0.7) | 83 (0.9) | 36 (1.2) | 291 (5.3) | 4259 (23.3) | 140 (4.0) |
| Psychosis | 327 (3.1) | 39 (0.4) | 27 (0.9) | 81 (1.5) | 1349 (7.4) | 24 (0.7) |
| Alcohol and drug abuse or dependence | 1121 (10.6) | 292 (3.2) | 85 (2.7) | 519 (9.4) | 1776 (9.7) | 144 (4.1) |
| Delirium | 248 (2.4) | 36 (0.4) | 11 (0.4) | 45 (0.8) | 328 (1.8) | 21 (0.6) |
| Dementia | 566 (5.4) | 63 (0.7) | 106 (3.4) | 35 (0.6) | 925 (5.1) | 29 (0.8) |
| Other psychiatric disorders | 544 (5.2) | 314 (3.5) | 86 (2.8) | 630 (11.5) | 2535 (13.9) | 298 (8.4) |
| Use of other psychotropic medications | | | | | | |
| Antidepressants | 2279 (21.6) | 3840 (42.3) | 1030 (33.2) | 3666 (66.7) | 10 130 (55.4) | 1795 (50.9) |
| Lithium | 20 (0.2) | 35 (0.4) | 33 (1.1) | 97 (1.8) | 867 (4.7) | 48 (1.4) |
| Antipsychotics | 531 (5.0) | 439 (4.8) | 116 (3.7) | 752 (13.7) | 4601 (25.1) | 262 (7.4) |
| Analgesics | 4172 (39.6) | 6575 (72.4) | 1153 (37.1) | 3307 (60.2) | 6647 (36.3) | 1921 (54.5) |

^aSix months prior to index date.**Table 3.** Study Population, Follow-up, and Event Rates

| | Participants, No. | Treatment Episodes, No. | Follow-up, d | | Events Within 180 d, No. (Incidence Rate per 1000 Person-Years) ^a | | | |
|-------------------------|-------------------|-------------------------|--------------|--------------|--|----------------------------|--|---|
| | | | Mean (SD) | Median (IQR) | Attempted Suicide (n = 801) | Completed Suicide (n = 26) | Attempted or Completed Suicide (n = 827) | Attempted or Completed Suicide or Violent Death (n = 868) |
| | | | | | | | | |
| Topiramate ^b | 52 127 | 57 853 | 97 (54) | 60 (60-152) | 109 (7.1) | 2 (0.1) | 111 (7.2) | 115 (7.4) |
| Carbamazepine | 8778 | 9859 | 87 (51) | 60 (60-120) | 20 (8.6) | 1 (0.4) | 21 (9.0) | 21 (9.0) |
| Ethosuximide | 42 | 47 | 77 (45) | 60 (60-60) | 0 | 0 | 0 | 0 |
| Felbamate | 13 | 15 | 101 (63) | 66 (60-181) | 0 | 0 | 0 | 0 |
| Gabapentin | 130 698 | 142 865 | 85 (49) | 60 (60-111) | 228 (6.9) | 8 (0.2) | 235 (7.1) | 250 (7.5) |
| Lamotrigine | 20 062 | 22 256 | 109 (58) | 98 (60-181) | 174 (26.1) | 7 (1.0) | 181 (27.1) | 186 (27.9) |
| Levetiracetam | 3544 | 3975 | 95 (54) | 60 (60-146) | 10 (9.7) | 0 | 10 (9.7) | 11 (10.7) |
| Oxcarbazepine | 7725 | 8579 | 98 (54) | 67 (60-154) | 75 (32.6) | 1 (0.4) | 76 (33.0) | 79 (34.3) |
| Phenobarbital | 1859 | 2130 | 73 (50) | 60 (37-90) | 4 (9.4) | 0 | 4 (9.4) | 4 (9.4) |
| Phenytoin | 9833 | 10 531 | 98 (56) | 66 (60-164) | 18 (6.4) | 1 (0.4) | 19 (6.7) | 20 (7.1) |
| Pregabalin | 7875 | 9086 | 76 (46) | 60 (50-97) | 9 (4.7) | 0 | 9 (4.7) | 12 (6.3) |
| Primidone | 2871 | 3104 | 95 (54) | 60 (60-150) | 2 (2.5) | 1 (1.2) | 3 (3.7) | 5 (6.2) |
| Tiagabine | 4853 | 5497 | 88 (49) | 60 (60-120) | 38 (28.7) | 0 | 38 (28.7) | 39 (29.5) |
| Valproate | 16 692 | 18 295 | 92 (52) | 60 (60-127) | 107 (23.2) | 5 (1.1) | 112 (24.3) | 118 (25.6) |
| Zonisamide | 2965 | 3528 | 90 (50) | 60 (60-120) | 7 (8.0) | 0 | 7 (8.0) | 8 (9.2) |

Abbreviation: IQR, interquartile range.

^aAs-treated analysis censoring at termination of health plan eligibility, treatment discontinuation, drug switching, event, or 180 days, whichever came first.^bReference drug.

therapy time. There were 827 attempted or completed suicides and a total of 868 combined events inclusive of attempted or completed suicides or vio-

lent deaths within 180 days after the initiation of any anticonvulsant medication.

The risk of attempted suicide, attempted or completed suicide, and any

suicidal event or violent death within 180 days among other anticonvulsant new treatment episodes compared with topiramate is shown in TABLE 4. Results of the multivariate-adjusted Cox regression analysis indicated that the risk for all outcomes was increased for gabapentin, lamotrigine, oxcarbazepine, tiagabine, and valproate new treatment use compared with topiramate use. In particular, the risk of attempted or completed suicide was meaningfully increased for gabapentin (hazard ratio [HR], 1.42; 95% CI, 1.11-1.80), lamotrigine (HR, 1.84; 95% CI, 1.43-2.37), oxcarbazepine (HR, 2.07; 95% CI, 1.52-2.80), tiagabine (HR, 2.41; 95% CI, 1.65-3.52), and valproate (HR, 1.65; 95% CI, 1.25-2.19). Similar results were obtained in the analysis evaluating any suicidal event or violent death. The first exposure within the exposure carried-forward 180 days analysis, which is less subject to potential bias due to informative switching or discontinuation, produced similar results (eTable 2). Extending the study period to 360 days of follow-up (eTable 3 and eTable 4) after drug initiation yielded no substantive differences from the 180-day analysis.

A secondary analysis using high-dimension propensity score matching confirmed the findings of the analysis for gabapentin, oxcarbazepine, and tiagabine treatment compared with topiramate episodes with regard to attempted or completed suicide and combined suicidal acts or violent death (eTables 5, 6, and 7). In particular, the risk of attempted or completed suicide was increased for gabapentin (RR, 1.99; 95% CI, 1.45-2.73; RD, 5.59 per 1000 person-years; 95% CI, 3.01-8.17 per 1000 person-years), oxcarbamazepine (RR, 1.49; 95% CI, 1.01-2.20; RD, 10.00 per 1000 person-years; 95% CI, 0.35-19.65 per 1000 person-years), and tiagabine (RR, 1.98; 95% CI, 1.15-3.41; RD, 14.06; 95% CI, 2.97-25.15 per 1000 person-years) (eTable 6).

In the high-dimension propensity score analysis, lamotrigine treatment episodes had a higher risk than topiramate for suicidal events. New treatment with

Table 4. Hazard Ratios of Study Outcomes Within 180 Days^a

| | HR (95% CI) | | |
|---|------------------|--------------------------------|---|
| | Suicide Attempt | Attempted or Completed Suicide | Attempted or Completed Suicide or Violent Death |
| Unadjusted analysis | | | |
| Carbamazepine | 1.18 (0.73-1.90) | 1.22 (0.76-1.94) | 1.18 (0.74-1.87) |
| Gabapentin | 0.94 (0.75-1.18) | 0.95 (0.76-1.19) | 0.98 (0.79-1.22) |
| Lamotrigine | 3.81 (3.00-4.85) | 3.90 (3.08-4.94) | 3.86 (3.06-4.87) |
| Levetiracetam | 1.37 (0.72-2.62) | 1.34 (0.70-2.57) | 1.43 (0.77-2.65) |
| Oxcarbazepine | 4.62 (3.45-6.20) | 4.60 (3.44-6.16) | 4.61 (3.47-6.14) |
| Phenobarbital | 1.26 (0.47-3.43) | 1.24 (0.46-3.36) | 1.20 (0.44-3.26) |
| Phenytoin | 0.91 (0.55-1.50) | 0.94 (0.58-1.53) | 0.96 (0.60-1.54) |
| Pregabalin | 0.64 (0.32-1.26) | 0.63 (0.32-1.24) | 0.81 (0.45-1.47) |
| Primidone | 0.35 (0.09-1.41) | 0.51 (0.16-1.61) | 0.83 (0.34-2.02) |
| Tiagabine | 3.96 (2.73-5.72) | 3.88 (2.69-5.61) | 3.85 (2.68-5.54) |
| Valproate | 3.25 (2.49-4.24) | 3.33 (2.56-4.34) | 3.39 (2.63-4.39) |
| Zonisamide | 1.11 (0.52-2.39) | 1.09 (0.51-2.34) | 1.21 (0.59-2.47) |
| Age-, sex-, and calendar year-adjusted analysis | | | |
| Carbamazepine | 1.38 (0.85-2.22) | 1.38 (0.87-2.21) | 1.32 (0.83-2.11) |
| Gabapentin | 1.52 (1.20-1.92) | 1.48 (1.17-1.87) | 1.49 (1.18-1.87) |
| Lamotrigine | 3.51 (2.76-4.48) | 3.58 (2.82-4.56) | 3.56 (2.81-4.50) |
| Levetiracetam | 1.63 (0.85-3.12) | 1.57 (0.82-3.01) | 1.65 (0.89-3.06) |
| Oxcarbazepine | 3.94 (2.92-5.32) | 3.88 (2.88-5.22) | 3.90 (2.92-5.22) |
| Phenobarbital | 1.61 (0.59-4.37) | 1.54 (0.57-4.17) | 1.46 (0.54-3.96) |
| Phenytoin | 1.24 (0.75-2.05) | 1.23 (0.75-2.01) | 1.22 (0.76-1.97) |
| Pregabalin | 1.37 (0.69-2.73) | 1.30 (0.65-2.59) | 1.59 (0.87-2.92) |
| Primidone | 0.78 (0.19-3.16) | 1.08 (0.34-3.42) | 1.62 (0.66-3.99) |
| Tiagabine | 4.58 (3.15-6.66) | 4.38 (3.02-6.36) | 4.30 (2.98-6.22) |
| Valproate | 3.10 (2.35-4.08) | 3.11 (2.37-4.07) | 3.15 (2.42-4.10) |
| Zonisamide | 1.19 (0.56-2.56) | 1.16 (0.54-2.50) | 1.28 (0.63-2.62) |
| Adjusted analysis ^b | | | |
| Carbamazepine | 1.23 (0.76-2.00) | 1.24 (0.77-1.99) | 1.19 (0.74-1.91) |
| Gabapentin | 1.44 (1.13-1.83) | 1.42 (1.11-1.80) | 1.42 (1.12-1.80) |
| Lamotrigine | 1.79 (1.38-2.31) | 1.84 (1.43-2.37) | 1.86 (1.45-2.39) |
| Levetiracetam | 1.71 (0.88-3.31) | 1.63 (0.84-3.16) | 1.66 (0.88-3.14) |
| Oxcarbazepine | 2.09 (1.54-2.85) | 2.07 (1.52-2.80) | 2.12 (1.57-2.86) |
| Phenobarbital | 1.05 (0.38-2.88) | 0.99 (0.36-2.72) | 0.96 (0.35-2.63) |
| Phenytoin | 1.26 (0.72-2.20) | 1.25 (0.73-2.15) | 1.19 (0.70-2.02) |
| Pregabalin | 1.22 (0.61-2.45) | 1.18 (0.59-2.37) | 1.44 (0.78-2.67) |
| Primidone | 0.83 (0.20-3.47) | 1.15 (0.35-3.78) | 1.84 (0.71-4.72) |
| Tiagabine | 2.49 (1.70-3.64) | 2.41 (1.65-3.52) | 2.40 (1.65-3.49) |
| Valproate | 1.65 (1.25-2.20) | 1.65 (1.25-2.19) | 1.69 (1.29-2.23) |
| Zonisamide | 1.28 (0.60-2.75) | 1.25 (0.58-2.69) | 1.37 (0.67-2.81) |

Abbreviations: CI, confidence interval; HR, hazard ratio.

^aAs-treated analysis censoring at termination of health plan eligibility, treatment discontinuation, drug switching, event, or 180 days, whichever came first. Reference is topiramate.

^bHazard ratios were adjusted in a Cox proportional hazard regression for age, sex, calendar year, initiation of anticonvulsant medication, depression, manic disorder, psychotic disorder, anxiety, alcohol abuse or dependence, drug abuse or dependence, delirium, dementia, personality disorder, sleep disorder, other psychiatric disorder, epilepsy, seizure disorder, neuropathy and neuropathic pain, migraine, tremor, multiple sclerosis, head injury, Parkinson disease, amyotrophic lateral sclerosis, number of medications, previous hospitalization, previous ambulatory visit, previous hospitalization for epilepsy or seizure disorder, previous hospitalization for mood disorder, previous hospitalization for any psychiatric disorder, antidepressants, lithium, antipsychotics, anxiolytics, analgesics, migraine medications, hypnotics, other psychotropic medications, myocardial infarction or revascularization procedure, cerebrovascular disease, other cardiovascular disease, diabetes mellitus, chronic lung disease, hypothyroidism, osteoarthritis or rheumatoid arthritis, gastrointestinal hemorrhage and inflammatory disease, liver cirrhosis and chronic disease, renal failure and other renal disease, and blood disorder.

valproate was no longer associated with a higher rate for suicidal events.

Kaplan-Meier curves comparing the time to attempted or completed suicide within 180 days showed increased risk for suicidal events beginning within the first 30 days after treatment initiation for gabapentin (HR, 1.68; 95% CI, 1.12-2.52), lamotrigine (HR, 2.45; 95% CI, 1.60-3.76), oxcarbazepine (HR, 2.79; 95% CI, 1.70-4.55), and tiagabine (HR, 3.57; 95% CI, 2.02-6.33) new treatment episodes (FIGURE 2) (eTable 8).

Gabapentin treatment was significantly associated with higher risk of suicidal events and combined suicidal acts or violent deaths in adults and young adults (eFigure, available at <http://www.jama.com>), while gabapentin, lamotrigine, oxcarbazepine, and tiagabine were associated with higher risk

among adults. Gabapentin, oxcarbazepine, and tiagabine were associated with increased risk among patients with mood disorder. A subgroup of patients with a recorded diagnosis of epilepsy or seizure disorders did not produce interpretable estimates because of the scarcity of events in the propensity score–matched analysis with topiramate as the reference drug.

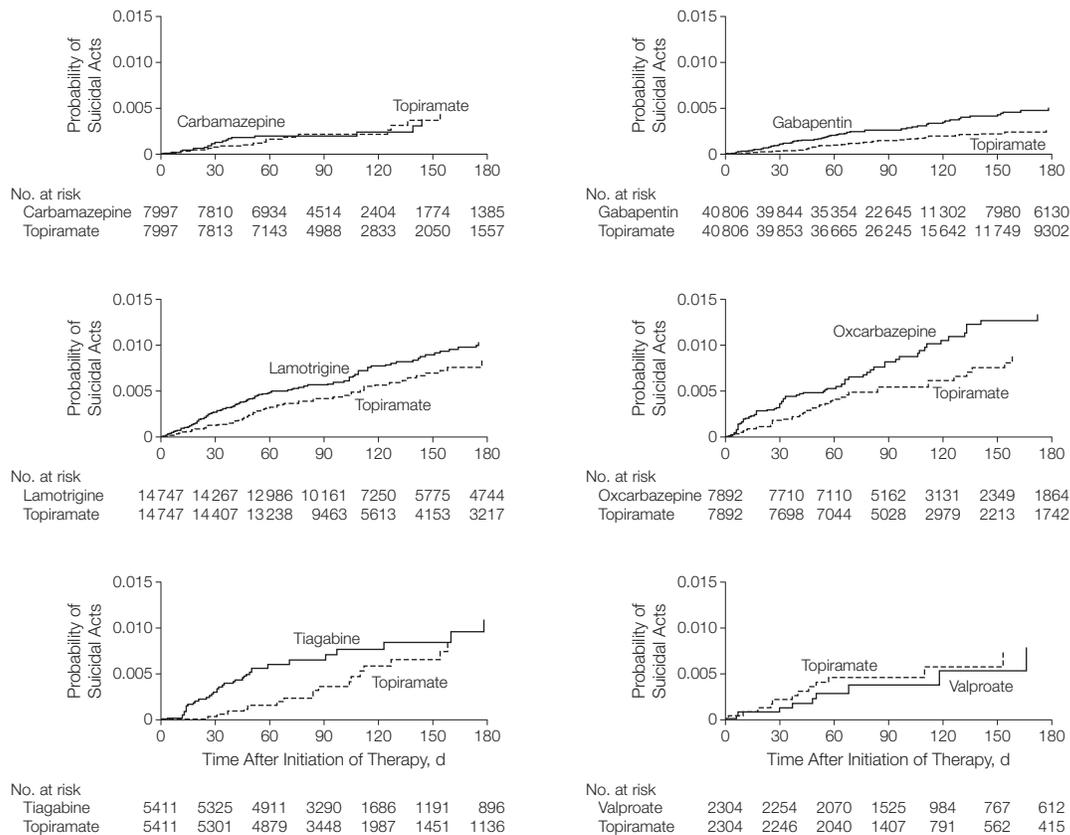
The propensity score–matched analysis with carbamazepine as the reference drug produced results qualitatively consistent with these findings, confirming an increased risk of suicidal events for patients beginning to take gabapentin, lamotrigine, oxcarbazepine, and tiagabine (eTable 9). In particular, we found a meaningful association between gabapentin and suicidality risk within 180 days among patients with recorded di-

agnosis of epilepsy or seizure disorders (RR, 13.92; 95% CI, 1.82-106.38) (eTable 10).

COMMENT

In a cohort analysis that evaluated 827 suicidal acts (801 attempted suicides and 26 completed suicides) and an additional 41 violent deaths (868 combined suicidal acts or violent deaths) in 297 620 new treatment episodes of anticonvulsant medications, we found an increased risk for these events in new users of gabapentin, lamotrigine, oxcarbazepine, and tiagabine compared with topiramate. A secondary analysis confirmed the increased risk and identified an excess of 5.6 cases of attempted or completed suicide per 1000 person-years among new users of gabapentin, 10.0 cases per 1000 person-

Figure 2. Adjusted Kaplan-Meier Plots for Time to Attempted or Completed Suicide After the Initiation of Selected Anticonvulsant Medications



High-dimension propensity score matching was used for adjustment. The primary as-treated analysis censored patient data at medication discontinuation or switching or at 180 days, whichever came first. "Suicidal acts" refers to attempted or completed suicides.

years among new users of oxcarbazepine, and 14.1 cases per 1000 person-years among new users of tiagabine compared with topiramate. The risk remained increased for gabapentin in subgroups of younger and older patients, patients with mood disorder, and patients with epilepsy or seizure disorders, although there were few events in the last group.

These findings are compatible with the results of the FDA meta-analysis, which found similarly increased risks of suicidal behavior or ideation for all anticonvulsant drugs compared with placebo, although its small numbers made it difficult to quantify these specific risks with confidence. No prior studies have directly evaluated the relationship between different anticonvulsant medications and risk of suicide in routine care. The few investigations addressing the issue were generally limited to patients with bipolar disorder, estimating the suicidal risk for anticonvulsant medications compared with lithium.²⁶⁻²⁸ In particular, a study of 12 662 Medicaid patients diagnosed with bipolar disorder found a meaningfully increased risk for completed suicide (HR, 2.6) among gabapentin users compared with lithium users.²⁸ However, the number of suicides identified was limited, and risk estimates were imprecise.

Anticonvulsant medications can have psychotropic effects, including mood and behavior changes.²⁹⁻³² However, there is no clear understanding of a possible mechanism of action that could lead to suicidal behavior in patients taking these medications; the existing theories are not consistent and often derive from small trials generally performed against placebo in populations mainly including epileptic patients.³²⁻³⁵ Gabapentin and lamotrigine, although they can have anxiolytic and mood stabilizer properties, have also been associated with behavioral problems such as aggression and hyperactivity, particularly in children and adults with learning disabilities and cognitive impairment.³⁶⁻⁴⁰ Tiagabine has been found to produce nervousness and depressive mood in placebo-controlled trials,^{41,42} po-

tentially leading to increased risk for suicidality.³⁵ Few data are available on the psychotropic effects of oxcarbazepine, but a stimulant effect on psychomotor functioning compared with placebo has been observed.⁴³

Anticonvulsant therapy is usually started at low dosages and increased according to the patient response, often requiring a few weeks to reach the average target dose.^{44,45} We found increased risk for suicidal acts beginning within the first 14 days after treatment initiation, opening the possibility that anticonvulsant medications could induce behavioral effects prior to the achievement of their full therapeutic effectiveness.

Although we used multiple approaches in the design and analysis of the study, including a new user design, multivariate-adjusted Cox proportional hazards models, and a high-dimension propensity score-matched analysis, residual confounding by indication is still a factor to consider. Patients beginning to take lamotrigine, oxcarbazepine, and tiagabine at baseline had a higher proportion of diagnosis and treatment for depressive and manic depressive disorders than the reference group. If the presence or the severity of such clinical conditions were incompletely controlled for, this could lead to residual confounding. This pattern was not identifiable for gabapentin; its users had a higher proportion of neuropathic pain and use of pain medications. Pain could also play an important role in the process leading to suicidal behavior. The analysis with carbamazepine as a reference drug confirmed an increased risk of suicidal acts for gabapentin, with a meaningful association among patients with a diagnosis of epilepsy or seizure disorders.

The coding for suicides and suicide attempts, critical for the definition of the study outcomes, may be subject to some misclassification. If this misclassification would be nondifferential, it would result in a bias towards the null. Anticonvulsant drug switching might be related to the effect on mood of the previous anticonvulsant medication. This could make switching a predictor for sui-

cidal acts that would not be observed in an as-treated analysis, therefore introducing bias toward the null. To minimize this potential bias, we additionally carried the first exposure forward similar to an intention-to-treat analysis without considering either drug discontinuation or switching. The results of this analysis were quite similar.

A final study limitation is the exploratory nature of this investigation. The fact that no previous studies have directly evaluated the relationship between different anticonvulsant medications and risk of suicide in routine care, the large sample size used, and the access to detailed patient information make this investigation valuable to clinical practice.

This exploratory analysis contributes to the understanding of the complex and little-understood relationship between anticonvulsant medication use and suicide risk. It suggests that the use of gabapentin, lamotrigine, oxcarbazepine, and tiagabine, compared with the use of topiramate or carbamazepine, may be associated with an increased risk of suicidal acts and combined suicidal acts or violent deaths.

Author Contributions: Dr Patorno had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Patorno, Bohn, Wahl, Avorn, Patrick, Schneeweiss.

Acquisition of data: Patorno, Bohn, Wahl, Avorn, Schneeweiss.

Analysis and interpretation of data: Patorno, Bohn, Wahl, Liu, Schneeweiss.

Drafting of the manuscript: Patorno, Schneeweiss. *Critical revision of the manuscript for important intellectual content:* Patorno, Bohn, Wahl, Avorn, Patrick, Liu, Schneeweiss.

Statistical analysis: Patorno, Bohn, Wahl, Patrick, Liu, Schneeweiss.

Obtained funding: Bohn, Avorn, Schneeweiss.

Administrative, technical, or material support: Bohn, Schneeweiss.

Study supervision: Bohn, Schneeweiss.

Financial Disclosures: Dr Bohn and Mr Wahl reported being employed by HealthCore Inc, a subsidiary of WellPoint, through the study execution. Dr Bohn reported that she has recently left the company and works as an independent consultant. Dr Schneeweiss reported being a paid member of the scientific safety advisory boards of HealthCore Inc and ii4sm; being a paid consultant to HealthCore, World Health Information Science Consultants, and RTI International; and having received an investigator-initiated research grant on the safety of nonsteroidal anti-inflammatory drugs from Pfizer. No other disclosures were reported.

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Role of the Sponsor: HealthCore had no role in the design and conduct of the study; in the analysis and interpretation of the data; or in the preparation, review, or approval of the manuscript.

Online-Only Material: eTables 1 through 10 and an eFigure are available at <http://www.jama.com>.

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text) is inaccurate, since their study did not demonstrate a statistically significant inverse association between vitamin B₆ intake and colorectal cancer risk.

PLP is not identical to vitamin B₆,^{2,3} and what is ingested is not equal to what will be in the blood.³ This may be one of the reasons that the authors chose to investigate associations with blood PLP level. I believe that what are needed are not only "large randomized clinical trials of vitamin B₆ supplementation," as the authors suggested, but also investigation of the gaps between vitamin B₆ and blood PLP with their corresponding biological effects. Factors interfering with the transformation of vitamin B₆ to PLP may possibly have direct or indirect effects on colorectal cancer risk.

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In Reply: We agree with Dr Lu that blood PLP levels are not identical to dietary vitamin B₆ intake. Blood PLP level is a more accurate and direct measure of PLP exposure. That is indeed one of the reasons why we chose to investigate blood PLP levels in relation to risk of colorectal cancer. As Lu points out, the conclusion in the Abstract could have been made more accurate by stating that blood PLP level but not vitamin B₆ intake had a statistically significant inverse association with risk of colorectal cancer in this meta-analysis.

A potential explanation for the lack of inverse association between vitamin B₆ intake and colorectal cancer in some studies may be because estimated vitamin B₆ intake

poorly predicted metabolically active PLP in those study populations. Measurement errors are inherent in food-frequency questionnaires, leading to misclassification of PLP exposure and attenuated risk estimates. The correlation between vitamin B₆ intake and PLP levels is also affected by factors such as malabsorption syndromes, impaired renal function, chronic alcoholism, and certain drugs.¹ We agree with Lu that the gap between vitamin B₆ intake and blood PLP levels merits further study. Moreover, there is a need for more studies on the interaction between vitamin B₆ and polymorphisms of genes encoding enzymes involved in the metabolism of vitamin B₆ in relation to colorectal cancer risk.

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CORRECTION

Incorrect Sentence in Text and Mislabeled Values in Figure: In the Preliminary Communication entitled "Anticonvulsant Medications and the Risk of Suicide, Attempted Suicide, or Violent Death," published in the April 14, 2010, issue of *JAMA* (2010;303[14]:1401-1409), a sentence in the text included an incorrect drug and a figure labeled data incorrectly. On page 1407 in the third paragraph, the sentence should have read, "The propensity score-matched analysis with carbamazepine as the reference drug produced results qualitatively consistent with these findings, confirming an increased risk of suicidal events for patients beginning to take gabapentin, oxcarbazepine, and tiagabine (eTable 9)." On page 1407 in Figure 2, the numbers at risk for topiramate and valproate were switched (ie, valproate numbers at risk were 2304, 2246, 2040, 1407, 791, 562, and 415). The Kaplan-Meier plot is correct and all resulting risk estimates are correct. eTables 9 and 10 were corrected online April 29, 2010.