PRELIMINARY COMMUNICATION

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

Elisabetta Patorno, MD, MPH
Rhonda L. Bohn, MPH, ScD
Peter M. Wahl, MLA, MS
Jerry Avorn, MD
Amanda R. Patrick, MS
Jun Liu, MD, MS
Sebastian Schneeweiss, MD, ScD

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.

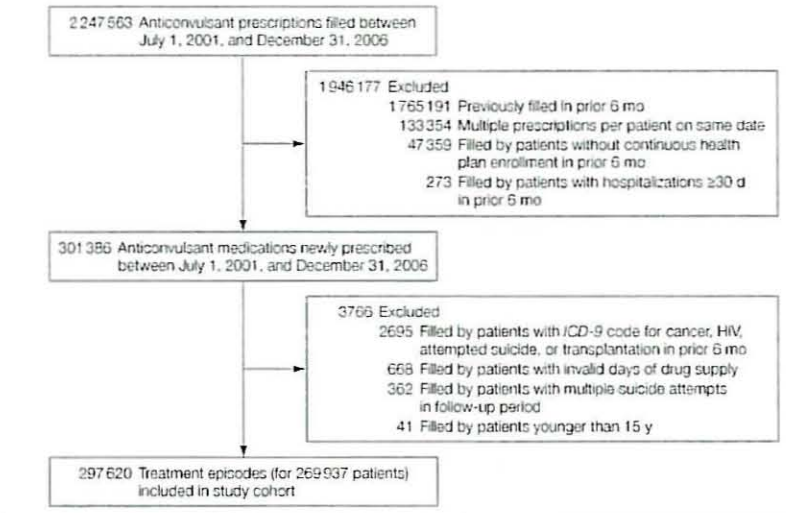
JAMA. 2010;303(14):1401-1409 www.jama.com

ANTICONVULSANT 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, prevented 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-

Author Affiliations: Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts (Drs Patorno, Bohn, Avorn, Liu, and Schneeweiss and Ms Patrick); and HealthCore Inc, Wilmington, Delaware (Dr Bohn and Mr Wahl).
Corresponding Author: Elisabetta Patorno, MD, MPH, Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, 1620 Tremont St, Ste 3030, Boston, MA 02120 (epatorno@partners.org).

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 number 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)

[a] Six 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	10531 (3.5)	9086 (3.1)	3104 (1.0)	5497 (1.9)	18295 (6.2)	3528 (1.2)
Demographics						
Female	4640 (44.1)	5419 (59.6)	1567 (50.5)	3320 (60.4)	10118 (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)	11876 (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)	10130 (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)

[a] Six months prior to index date.

Table 3. Study Population, Follow-up, and Event Rates

					Events Within 180 d, No. (Incidence Rate per 1000 Person-Years)[a]			
			Follow-up, d					
	Participants, No.	Treatment Episodes, No.	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]	52127	57853	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	130698	142865	85 (49)	60 (60-111)	228 (6.9)	8 (0.2)	235 (7.1)	250 (7.5)
Lamotrigine	20062	22256	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	10531	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	16692	18295	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.
[a] As-treated analysis censoring at termination of health plan eligibility, treatment discontinuation, drug switching, event, or 180 days, whichever came first.
[b] Reference drug.

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

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

[b] Hazard 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).

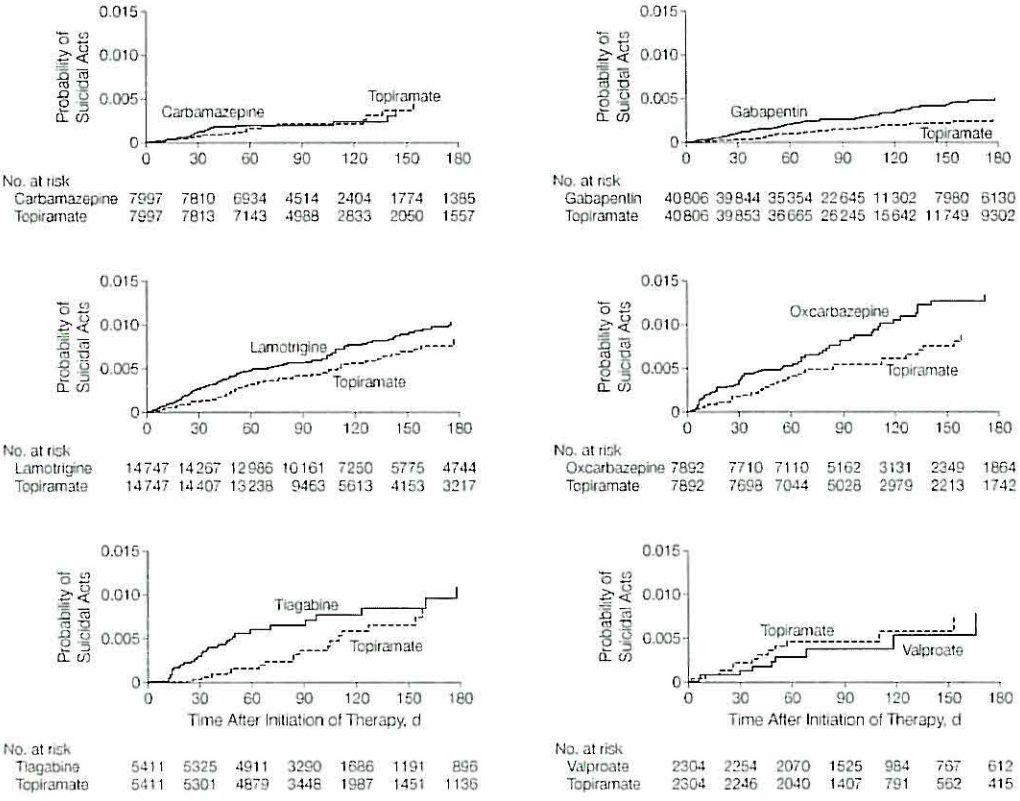
Gabapentin treatment was significantly associated with higher risk of suicidal events and combined suicidal acts or violent deaths in adults and young adults (eFigure, available at http://www.jama.com), while gabapentin, lamotrigine, oxcarbazepine, and tiagabine were associated with higher risk among 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 diagnosis 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] potentially 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 suicidal 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 i4sm; 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.
Funding/Support: This study was supported by the HealthCore Fellowship in Pharmacoepidemiology and the Pharmacoepidemiology Research and Training Fund of the Harvard School of Public Health (Dr Patorno).

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.

REFERENCES

1. Ettinger AB, Argoff CE. Use of antiepileptic drugs for nonepileptic conditions. *Neurotherapeutics*. 2007; 4(1):75-83.
2. Johannessen Landmark C. Antiepileptic drugs in non-epilepsy disorders. *CNS Drugs*. 2008;22(1):27-47.
3. Spina E, Perugi G. Antiepileptic drugs. *Epileptic Disord*. 2004;6(2):57-75.
4. Hamer AM, Haxby DG, McFarland BH, Ketchum K. Gabapentin use in a managed Medicaid population. *J Manag Care Pharm*. 2002;8(4):266-271.
5. Rosenberg JM, Salzman C. Update: new uses for lithium and anticonvulsants. *CNS Spectr*. 2007; 12(11):831-841.
6. Statistical review and evaluation: antiepileptic drugs and suicidality [May 23, 2008]. http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4372b1-01-FDA.pdf. Accessed December 4, 2009.
7. Joint meeting of the Peripheral and Central Nervous Drugs Advisory Committee and the Psychopharmacologic Drugs Advisory Committee: briefing material, July 10, 2008. http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4372b1-00-index.html. Accessed December 4, 2009.
8. FDA Public Health Advisory: suicidal thoughts and behavior anticonvulsant. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm100195.htm. Accessed December 4, 2009.
9. Update on suicidal behavior and ideation and anticonvulsant drugs: update May 5, 2009. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm100190.htm. Accessed December 4, 2009.
10. Avorn J. Drug warnings that can cause fits. *N Engl J Med*. 2008;359(10):991-994.
11. Ray WA. Evaluating medication effects outside of clinical trials. *Am J Epidemiol*. 2003;158(9): 915-920.
12. *International Classification of Diseases, Ninth Revision, Clinical Modification*. Washington, DC: US Dept of Health and Human Services. 1988.
13. Iribarren C, Sidney S, Jacobs DR Jr, Weisner C. Hospitalization for suicide attempt and completed suicide. *Soc Psychiatry Psychiatr Epidemiol*. 2000; 35(7):288-296.
14. Moyer LA, Boyle CA, Pollock DA. Validity of death certificates for injury-related causes of death. *Am J Epidemiol*. 1989;130(5):1024-1032.
15. Clark DE, DeLorenzo MA, Lucas FL, Wennberg DE. Epidemiology and short-term outcomes of injured Medicare patients. *J Am Geriatr Soc*. 2004; 52(12):2023-2030.
16. Patrick AR, Miller M, Barber CW, Wang PS, Canning CF, Schneeweiss S. Identifying intentional self-harm hospitalizations when E-codes are incompletely recorded. *Pharmacoepidemiol Drug Saf*. 2009; 18:S1-S273.
17. World Health Organization. *International Statistical Classification of Diseases, 10th Revision (ICD-10)*. Geneva, Switzerland: World Health Organization; 1992.
18. Phillips DP, Ruth TE. Adequacy of official suicide statistics for scientific research and public policy. *Suicide Life Threat Behav*. 1993;23(4):307-319.
19. Ohberg A, Lonnqvist J. Suicides hidden among undetermined deaths. *Acta Psychiatr Scand*. 1998; 98(3):214-218.
20. *Physicians' Current Procedural Terminology (CPT)*. 4th ed. Chicago, IL: American Medical Association; 1989.
21. Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Mogun H, Brookhart MA. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. *Epidemiology*. 2009; 20(4):512-522.
22. Parsons L. Reducing bias in a propensity score matched-pair sample using greedy matching techniques. In: Proceedings of the 26th Annual SAS Users Group International Conference. SAS Institute Inc, 2001. http://www2.sas.com/proceedings/sugi26/p214-26.pdf. Accessed March 22, 2010.
23. Austin PC, Lee DS. The concept of the marginally matched subject in propensity-score matched analyses. *Pharmacoepidemiol Drug Saf*. 2009; 18(6):469-482.
24. Rothman KJ. No adjustments are needed for multiple comparisons. *Epidemiology*. 1990;1(1):43-46.
25. Vandenbroucke JP. Observational research, randomised trials, and two views of medical science. *PLoS Med*. 2008;5(3):e67.
26. Goodwin FK, Fireman B, Simon GE, Hunkeler EM, Lee J, Revicki D. Suicide risk in bipolar disorder during treatment with lithium and divalproex. *JAMA*. 2003; 290(11):1467-1473.
27. Yerevanian BI, Koek RJ, Mintz J. Bipolar pharmacotherapy and suicidal behavior. *J Affect Disord*. 2007; 103(1-3):5-11.
28. Collins JC, McFarland BH. Divalproex, lithium and suicide among Medicaid patients with bipolar disorder. *J Affect Disord*. 2008;107(1-3):23-28.
29. Schmitz B. Effects of antiepileptic drugs on mood and behavior. *Epilepsia*. 2006;47(suppl 2):28-33.
30. Reijs R, Aldenkamp AP, De Krom M. Mood effects of antiepileptic drugs. *Epilepsy Behav*. 2004; 5(suppl 1):S66-S76.
31. Ettinger AB. Psychotropic effects of antiepileptic drugs. *Neurology*. 2006;67(11):1916-1925.
32. Mula M, Sander JW. Negative effects of antiepileptic drugs on mood in patients with epilepsy. *Drug Saf*. 2007;30(7):555-567.
33. Barabas G, Matthews WS. Barbiturate anticonvulsants as a cause of severe depression. *Pediatrics*. 1988;82(2):284-285.
34. Ketter TA, Post RM, Theodore WH. Positive and negative psychiatric effects of antiepileptic drugs in patients with seizure disorders. *Neurology*. 1999; 53(5)(suppl 2):53-67.
35. Kalinin VV. Suicidality and antiepileptic drugs: is there a link? *Drug Saf*. 2007;30(2):123-142.
36. Wolf SM, Shinnar S, Kang H, Gil KB, Moshé SL. Gabapentin toxicity in children manifesting as behavioral changes. *Epilepsia*. 1995;36(12):1203-1205.
37. Lee DO, Steingard RJ, Cesena M, Helmers SL, Riviello JJ, Mikati MA. Behavioral side effects of gabapentin in children. *Epilepsia*. 1996;37(1):87-90.
38. Tallian KB, Nahata MC, Lo W, Tsao CY. Gabapentin associated with aggressive behavior in pediatric patients with seizures. *Epilepsia*. 1996;37(5): 501-502.
39. Beran RG, Gibson RJ. Aggressive behaviour in intellectually challenged patients with epilepsy treated with lamotrigine. *Epilepsia*. 1998;39(3):280-282.
40. Ettinger AB, Weisbrot DM, Saracco J, Dhoon A, Kanner A, Devinsky O. Positive and negative psychotropic effects of lamotrigine in patients with epilepsy and mental retardation. *Epilepsia*. 1998;39(8):874-877.
41. Pereira J, Marson AG, Hutton JL. Tiagabine add-on for drug resistant partial epilepsy. *Cochrane Database Syst Rev*. 2002;3(3):CD001908.
42. Grabowska-Grzyb A, Jedrzejczak J, Naganska E, Fiszer U. Risk factors for depression in patients with epilepsy. *Epilepsy Behav*. 2006;8(2):411-417.
43. Curran HV, Java R. Memory and psychomotor effects of oxcarbazepine in healthy human volunteers. *Eur J Clin Pharmacol*. 1993;44(6):529-533.
44. French JA, Pedley TA. Clinical practice: initial management of epilepsy. *N Engl J Med*. 2008;359 (2):166-176.
45. Elger CE, Schmidt D. Modern management of epilepsy: a practical approach. *Epilepsy Behav*. 2008; 12(4):501-539.