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Gabapentin and Suicide Attempts

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Abstract

Purpose—On December 16, 2008 FDA issued a class warning for antiepileptic drugs and suicidal thoughts and behavior. The purpose of this study was to determine if the antiepileptic drug gabapentin increases risk of suicide attempt in patients to which it was prescribed for various indications.

Methods—We conducted a pharmacoepidemiologic study in which suicide attempt rates were compared before and after gabapentin was prescribed. We used the PharMetrics medical claims database to study the relationship between gabapentin and suicide attempts in a cohort of 131,178 patients with a one-year window of information before and after initial prescription. Patients had diagnoses of epilepsy, pain disorders, bipolar illness, major depressive disorder, schizophrenia, and other psychiatric disorders.

Results—Overall, there was no significant difference in suicide attempt rates before (3.48/1000 patient years - PY) versus after (3.45/1000 PY) gabapentin prescription. Pre-prescription suicide attempt rates were five times higher in psychiatric populations compared with non-psychiatric populations leading us to analyze the two groups separately. No drug effect was detected in the non-psychiatric populations. Significant reductions in suicide attempt rates were seen for bipolar disorder (47.85/1000 PY versus 31.46/1000 PY), major depressive disorder (17.30/1000 PY versus 12.66/1000 PY), and other psychiatric disorders (12.84/1000 PY versus 10.14/1000 PY). Person-time analysis revealed an overall significant reduction in suicide attempt rates (2.01/1000 PY on drug versus 2.30/1000 PY off drug).

Conclusions—This study finds that gabapentin does not increase risk of suicide attempts in non-psychiatric populations and is associated with a reduction in suicide attempt risk in patients with psychiatric disorders.

Keywords

gabapentin; suicide attempt; antiepileptic drugs; person-time logistic regression

Background

Anticonvulsant medications are life saving in the treatment of seizure disorders and also used for other indications such as mood disorders and chronic pain (trigeminal neuralgia, fibromyalgia, etc.) (Backonja, 1998). In March of 2005, FDA sent letters to sponsors of 11 antiepileptic drugs (AEDs) requesting the submission of suicidality data (suicidal thoughts, behavior, and completion, see Posner, 2007) from randomized placebo-controlled clinical trials. Based on FDA's analysis of these data, on January 31, 2008, an alert was issued to health care providers regarding increased risk of suicidal thoughts and behavior with AEDs (1). While details of the analysis were limited in the alert, on May 23, 2008, FDA released a report on the details of their statistical review and evaluation of these data (2). On July 10, 2008, an FDA scientific advisory committee voted "yes" that there was a significant positive association between AEDs and suicidality but voted against placing a black box warning on AEDs for suicidality. On December 16, 2008 FDA issued a label warning for heightened risk of suicidal thoughts and behavior for users of AEDs.

The primary analysis performed by the FDA to determine if a relationship between AEDs and suicidality exists was a fixed-effects meta-analysis that required removal of all studies with zero events in both arms. With an overall rate of suicidality events (thoughts and behaviors) of less than 0.5%, this led to the elimination of the majority of the data for many of the drugs. As an example, of the 49 studies of gabapentin submitted to the FDA, only 3 were included in FDA's primary meta-analysis (i.e., there were only 3 events out of 4932 observations that FDA used in their analysis). Based on these analyses, FDA concluded that there was an increased risk of suicidality for patients receiving AEDs relative to placebo (odds ratio (OR)=1.80, confidence interval (CI) 1.24–2.66, risk difference of 2.1 per 1000 more patients in the drug treated group experiencing suicidality relative to placebo) and concluded that "the results were generally consistent among all the different drug products."

Several recent pharmacoepidemiologic studies of suicide risk of AED treatment have been conducted (3–7). Collins and McFarland (3) compared suicide completion and attempt rates between lithium, gabapentin, divalproex, and carbamazepine in a cohort of 12,662 bipolar patients from an Oregon Medicaid medical claims database. There were 11 suicides and 79 attempts. Relative to lithium, divalproex had higher suicide attempt (SA) rates, and gabapentin had higher rates of suicide completion. The authors concluded that lithium may have protective effects; however it remained unclear whether or not lithium protects these patients against suicide completion. They also note that the difference between lithium and gabapentin in suicide rates could be due to confounding by indication, where gabapentin users may also suffer from chronic pain and be at even higher suicidal risk.

Patrono (4) conducted a cohort study of patients taking one of the 11 AEDs studied by FDA, which identified 26 completed suicides, 801 attempted suicides and 41 violent deaths in 297,620 new episodes of treatment. Prescriptions for gabapentin, lamotrigine, oxcarbazepine, tiagabine, and valproate were associated with higher rates of suicidal acts than their selected comparator topiramate.

Olesen (5) conducted nation-wide case-crossover and cohort studies to examine the relationship between AED use and completed suicide in Denmark. There were 6,780 cases of suicide over a 10-year period, of which 422 received AED treatment at the time of suicide. The case-crossover study compared rates of AED treatment within 30 days of suicide to two control periods (90–120 days and 60 to 90 days prior to suicide). Results of the case-crossover study revealed increased risk of suicide for patients treated with clonazepam, valproate, lamotrigine, and phenobarbital. The cohort study consisting of 169,725 AED treatment-naïve patients found similar results using carbamazepine as the

comparator. Neither analysis found a significant relationship between gabapentin and suicide.

Van Cott (6) used VA and Medicare databases to conduct a case-control study of AED (monotherapy) treatment and suicidal behavior in a cohort of veterans 66 years and older. The strongest predictor of suicidal behaviors was an affective disorder (depression, anxiety, or post-traumatic stress disorder - PTSD), that was diagnosed before AED treatment. Increased suicidal behavior was not associated with AED treatment. A trend was identified for the two newer AEDs (levetiracetam and lamotrigine) which were associated with higher rate of suicidal behavior relative to their selected comparator gabapentin (OR = 10.2, 95% CI = 1.1–97.0).

We (7) reported results of a large-scale pharmacoepidemiologic study of a cohort of 47,918 bipolar depressed patients taking AEDs, in which SA rates were compared before and after initial filled prescription and to a no medication comparison group (4). Analyses were restricted to AED and lithium monotherapy. Overall, there was no significant difference in SA rates for patients treated with an AED (13/1000 patient years (PY)) versus patients not treated with either an AED or lithium (13/1000). In AED treated subjects, the rate of SAs was significantly higher prior to initial filled prescription (72/1000) than after (13/1000). In patients receiving no concomitant antidepressant, other AED or antipsychotic medication, AED prescription was associated with significantly lower SA rates relative to untreated patients (3/1000 versus 15/1000). Person-time analyses revealed significantly reduced risk of SA during months in which an AED prescription was filled versus months without prescription coverage.

The purpose of this study is to provide a more detailed evaluation of gabapentin, one of the 11 AEDs studied by FDA, and to examine any association between gabapentin, and suicidality overall, and separately by various indications. Our analysis focuses exclusively on SAs and not suicidal thoughts which represented the primary events that formed the basis of FDA's analysis. Given the rarity of suicidal behavior in patients treated with AEDs we studied a cohort of 131,178 patients treated with gabapentin, with one year of continuous enrollment in a managed care program both before and after initial gabapentin prescription.

Methods

Data

Data for this study came from the PHARMetrics Patient Centric Database, the largest national patient-centric database of longitudinal integrated health care claims data commercially available from PHARMetrics®, Inc., under unrestricted license. These national data are not statistically different from the 2000 U.S. Census distributions of age, gender, and region. The universe of data are comprised of medical, specialty, facility, and pharmacy paid claims from more than 85 managed care plans nationally, representing more than 47 million covered lives.

Definition of Cohort and Suicide Attempt

Data were collected during fiscal years 2000 through 2006. All patients who received a filled prescription for gabapentin and had continuous enrollment in a participating health plan one year before and after the initial prescription were included. Analyses were conducted overall, and separately within relevant diagnostic groups (epilepsy, pain disorders, bipolar illness, major depressive disorder (MDD), schizophrenia, and other psychiatric disorders). Analyses also adjusted for age, sex, and concomitant pharmacologic treatment (other AEDs, antidepressants, antipsychotics, and lithium). A sensitivity analysis was also performed excluding patients who filled prescriptions for any of these concomitant

medications. The ICD 9 codes used to identify SAs were E950-E959, where subcategories are E950-E952 (self-inflicted poisoning), E953 (self-inflicted injury by hanging), E954 (drowning), E955 (self-inflicted injury by firearms), E956 (self-inflicted injury by cutting), E957 (self-inflicted injury by jumping from high places), E958 (other/unspecified self-inflicted injury), and E959 (late effects of self-inflicted injury).

Statistical Methods

Analysis of these data was based on a Poisson regression model where the rate of SA prior to and after the initial gabapentin prescription was filled could be compared. The method of generalized estimating equations (8) was used to accommodate the within-subject correlation. For the primary analysis, exposure was considered to be the entire year following dispensation of at least one gabapentin prescription. This is conservative because it attributes all SAs during the post-prescription initiation period to the drug, regardless of the length of the prescription. However, it also considers the exposure risk period to be 360 days, regardless of the length of actual exposure, which can dilute the effect of short-term exposures. This assumption is explored in a sensitivity analysis.

Results were expressed as event rate ratios (ERR) and associated confidence intervals (CI), which are the exponential of the estimated drug effect (and confidence interval) in the Poisson regression model. The ERR is a rate multiplier which reflects the change in rate of SAs following the initial prescription. An ERR of 1.0 means that there is no effect of gabapentin (i.e., the rates are identical). ERRs above 1.0 indicate increased risk associated with gabapentin and ERRs below 1.0 indicate decreased risk (e.g., ERR=2 indicates double the risk and ERR=0.5 indicates one-half the risk). Statistical significance of the ERR is determined by the Wald test and by determining if the CI contains the value 1.0. The Poisson model permits multiple SAs per individual.

As a sensitivity analysis we used a person-time logistic regression model (9–11), where gabapentin prescription was modeled as a time-varying covariate, and the hazard rate of SA was estimated on a month by month basis, adjusting for all previously described covariates, and SAs in the year prior to the initial gabapentin prescription. Unlike the previous analyses where exposure was considered to be one year for all subjects, in this analysis, prescription exposure was evaluated on a month by month basis. The number of days supply of the prescription was used to determine if the prescription covered additional months beyond the month in which the prescription was filled. This analysis determines the effects of duration and pattern of exposure on our overall conclusions. This model also adjusted for month, which allowed the risk of SA to change over time. This analysis does not differentiate single from multiple SAs from each subject, so it also provides a sensitivity analysis for the inclusion of multiple SAs for each subject in the primary analysis. The analysis was also repeated on patients who made a SA in the year prior to taking gabapentin and in patients with a psychiatric diagnosis.

Results

Descriptive Statistics

Characteristics of the sample are described in Table 1. Table 1 reveals that the bulk of the subjects had a pain disorder (107,816), and that for patients with epilepsy or psychiatric disorders (bipolar, MDD, schizophrenia, other), 70%–80% also had a concomitant pain disorder. Concomitant medication prescriptions were also relatively high, particularly among patients with psychiatric disorders. In particular, many of these patients received antidepressant medications in addition to gabapentin, although the rate was lower for pain

disorder patients (50%). Patients with epilepsy also had lower rates of concomitant antidepressant prescription.

In terms of age, the distribution was relatively homogeneous across the diagnostic groups with bipolar disorder and epilepsy patients being the youngest and pain disorder patients the oldest. With respect to sex, the majority of patients were female (63%), but females were even more highly represented among MDD and bipolar subpopulations (72% and 68% respectively).

Primary Analysis

Table 2 presents results of the statistical comparisons of SA rates before and after initial gabapentin prescription. Significant decreases in SA rates were observed for bipolar patients (ERR=0.62, CI=0.41–0.94, $p=0.026$) and for MDD patients (ERR=0.65, CI=0.52–0.82, $p<0.001$), and for other psychiatric disorders (ERR=0.69, CI=0.55–0.88, $p=0.002$). By contrast, no significant effects of prescription on SA rates were observed for epilepsy, pain disorder or schizophrenia, although schizophrenia had a similar ERR of 0.74 (0.41–1.35) to the other psychiatric disorders.

The overall effect of gabapentin on SA (obtained from a model that pooled all disorders, controlled for age, sex, and other drugs) was not significant (ERR=0.93, CI=0.76–1.14, $p=0.487$), which is consistent with the fact that the majority of patients were pain disorder patients for which there was no effect of prescription on SA rate. When the analysis was restricted to patients with psychiatric indications, a significant reduction in SAs following gabapentin prescription initiation was found (ERR=0.73, CI=0.59–0.90, $p=0.004$, 10.31/1000 PY pre versus 8.58/1000 PY post gabapentin). Finally, the analysis which excluded all patients who were prescribed any concomitant medication (i.e., an additional AED, antidepressant, lithium, or antipsychotic medication), also failed to identify any increased risk of SA associated with gabapentin prescription (ERR=0.53, CI=0.16–1.73, $p=0.294$). In fact, the rate of SAs was half following prescription initiation (0.16/1000 PY) relative to prior to prescription (0.30/1000 PY); however, this difference was not statistically significant given the much lower incidence of SAs in the gabapentin monotherapy sample.

Sensitivity Analysis

Results of the person-time logistic regression model revealed a significant overall effect of gabapentin use on SAs (OR=0.74, CI=0.56–0.97, $p<0.03$), indicating reduced risk of SAs while patients received a gabapentin prescription (see Figure 1). Following the initial prescription, the SA rate during months in which a prescription was filled was 2.01 per 1000 person years (78/38852) and 2.30 per 1000 person years (212/92326) during months in which a prescription was not filled. Similar results were found when the sample was restricted to patients with psychiatric diagnoses (OR=0.73, CI=0.54–0.99, $p<0.04$) although the overall rates were higher at 5.8 per 1000 person years off prescription and 4.9 per 1000 person years on prescription. In those patients who only were prescribed gabapentin (i.e., no other AED, lithium, antidepressant, or antipsychotic) there were only 6 SAs following prescription with gabapentin (6/56779) for an overall SA rate of 0.11 per 1000 person years. All 6 of these SAs were off drug (6/42240) and none occurred during months in which a prescription for gabapentin was filled (0/14539). Note that these rates are lower than those reported in Table 1 for the primary analysis because they only consider a single SA per patient.

Prior Attempters

In the 271 patients who made a SA in the year prior to initiating gabapentin prescription, a person-time logistic regression analysis revealed a statistically non-significant decreased rate

of SAs associated with prescription (OR=0.71, CI=0.32–1.57, $p<0.40$). On prescription, the SA rate was 129 per 1000 PY, whereas off prescription the rate was 140 per 1000 PY.

Discussion

These findings reveal that in this cohort of over 130,000 patients treated with gabapentin, there is no overall increased risk of SA associated with gabapentin. Gabapentin does not increase the likelihood of SAs, and the SAs considered here were of sufficient severity to make it into the medical record. However, among patients with a psychiatric disorder, who are at increased suicidal risk, statistically significant decreases in the rate of SAs were observed following gabapentin prescription. Indeed, the pre-prescription SA rate for patients with bipolar disorder was 48 per 1000 PY as compared to only 3 per 1000 PY for patients with pain disorder. Following prescription, however, the SA rate decreased to 32 per 1000 PY in bipolar patients (a 33% decrease), but remained constant at 3 per 1000 PY for pain disorder patients. These findings suggest that among those patients at increased risk of SAs, gabapentin may have a protective effect. Whether this effect is based on reducing the symptoms of the psychiatric disorder or by treating the concomitant pain disorder that is present in many of these patients remains an open question. The absence of a significant association between gabapentin and SA in patients receiving a prescription for pain disorder suggests that having comorbid psychiatric and pain disorders may greatly elevate SA risk, which significantly decreases if the pain disorder is successfully treated with gabapentin. Given the high rate of concomitant pain disorder in psychiatric patients receiving gabapentin, it is likely that gabapentin was prescribed for the pain disorder and not for the psychiatric disorder.

Analysis of gabapentin monotherapy patients (i.e., no concomitant AED, antidepressant, antipsychotic or lithium), revealed that the annual SA rate among patients taking gabapentin alone is in fact quite low (16/100,000); however, it is almost twice as high in these same patients prior to receiving a prescription for gabapentin (30/100,000). The patients in this monotherapy cohort, are primarily patients being treated for pain. Elevated SA rates among patients who receive gabapentin are associated with psychiatric illness and concomitant medications are markers for greater severity of illness, non-response to treatment, and/or diagnostic comorbidities, all of which increase suicidal risk. Gabapentin decreases SA rates in these more severely ill patients with psychiatric comorbidities. Gabapentin also appears to decrease the already low SA rate in the least severely ill patients who received gabapentin alone. No evidence was found for increased risk of SA associated with gabapentin.

Person-time logistic regression revealed significant reductions in SA rates with gabapentin prescription. Furthermore in the highest risk patients who had made a SA in the previous year, reduction in the rate of SAs was also observed; however, it was not statistically significant due to the small sample size (i.e., $n=271$ patients). Remarkably, the rate of SAs following prescription was over 50 times higher in this high risk sample than in the overall sample (i.e., 137 per 1000 PY). This is a segment of the population that is rarely if ever studied in randomized controlled clinical trials.

Unlike the primary pre-prescription versus post-prescription analyses which considered all of the SAs during the post-prescription year to be attributed to prescription, the person-time analyses restrict exposure to only those months during which the patient had filled a prescription. Inspection of the raw data reveals that the SA rate is higher during those months when the patient was not being treated with gabapentin. This may account for why overall significant decreases in SA rates were found in these analyses (and not the overall primary analysis), which appeared to be similar in psychiatric and non-psychiatric indications.

With respect to gabapentin, FDA performed two separate analyses. First, as part of their primary analysis, they computed a gabapentin-specific odds ratio of 1.57 (0.12–47.66). The confidence interval clearly includes 1.0 and is extremely wide, which at first examination might suggest that the true OR could indicate that gabapentin is either safe, very protective or very harmful. In fact, the width of the confidence interval is due to the fact that in FDA's primary analysis, there were only 3 events (all ideation), 2 for gabapentin and 1 for placebo in a total of 4932 patients. Second, as a sensitivity analysis, FDA conducted a meta-analysis of risk differences, which did not require the exclusion of zero-event studies. Here, FDA found that for gabapentin, the estimated risk difference was only 0.28 suicidal thoughts per 1000 patients (i.e., one quarter of a patient more experiencing a suicidal thought treated with gabapentin relative to placebo), with a base rate in the placebo condition of 0.49 per 1000 patients. The confidence interval for this rate difference ranged from -1.37 to 1.92, indicating that the effect was not statistically different from placebo, and here the confidence interval for the risk difference is reasonably narrow. In summary, neither of FDA's gabapentin specific analysis gave any support to increased risk of suicidal ideation relative to placebo, and no SAs were reported.

Results of our study differ from those described by Paterno (4) who found increased risk of suicidal acts for gabapentin relative to topiramate. However, their analysis was restricted to between drug comparisons. Drug use groups were compared using both covariate adjustment and 1:1 propensity score matching strategies. The assumption of these analyses is that following statistical adjustment, patients taking different drugs are comparable in terms of suicidality risk. This is a very difficult assumption to verify. Using a similar approach, we (7) found that balance in observed covariates was achieved using propensity score matching but SA rates before AED prescription fills remained elevated in patients who were ultimately prescribed an AED versus those that did not receive AED treatment. There is no possible way that this residual difference could be drug related (since it occurred prior to drug therapy), and therefore represents an example of hidden bias (12). The absence of an untreated control group limits inferences that can be drawn from their study with respect to increased risk of suicidality with AED treatment.

There are several limitations of our study. First, our results are based on medical claims data and there is likely to be under-reporting of SAs. Second, we do not have access to information on completed suicides in this population. Third, our analyses do not incorporate intensity of treatment. Fourth, patients were not randomized to treatment, and there may be other factors that play a significant role in the process by which specific treatments are selected for patients. Fifth, diagnoses were obtained from electronic data systems and not from structured psychiatric interviews. Sixth, our analyses do not consider treatment adherence or dosage levels, which may play an important role in suicidal behavior. While these limitations can all lead to biased estimates of the incidence of SAs, it is unclear how they would lead to biased estimates of the pre versus post-treatment difference in SA rate. Furthermore, the person-time analyses directly adjust for the natural decay (regression effect) in SA rate over time and incorporate information regarding the actual pattern of gabapentin use over time.

The findings of this study are noteworthy because of the large number of SAs. There were a total of 909 SAs during the two year observation period. By contrast, in FDA's analysis, there were only 38 SAs for all 11 AEDs, none of which were for gabapentin. This may explain some of the discrepancy between FDA's findings and those of the present study and previous published report (4).

Finally, these data shed light on the question of representativeness of RCTs to routine clinical practice. There were a total 38 SAs out of 43,892 patients included in FDA's meta-

analysis. The average duration of these trials was 90 days, so there were approximately 10,973 PY yielding a rate of 3.46/1000 PY. The overall SA rate in our study was 3.45/1000 PY, suggesting that at least in this population using these medications, the RCTs do reflect the SA rate observed in the general population.

Key Points

- Gabapentin did not increase risk of suicide attempts for any indication
- Significant reductions in suicide attempt rates were seen for patients with psychiatric disorders.
- Person-time analysis revealed an overall significant reduction in suicide attempt rates with gabapentin prescription.

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Figure 1.
Hazard Functions for Suicide Attempts over Time. Comparison of Gabapentin to no Gabapentin

Table 1

Summary Statistics (Mean and Percent) by Diagnosis

Diagnosis	# of Subjects	Mean (std)	Other										
			Age	Male	Bipolar	Epilepsy	MDD	Pain	Psych	Schiz	Anticonv	Antidepr	Antipsyc
Bipolar Disorder	3,783	40.4 (13.9)	31.7			1.9	56.3	70.9	65.9	5.8	60.4	80.3	48.6
Epilepsy	1,411	41.8 (17.8)	40.2		5.0		26.9	72.0	42.3	1.2	72.4	48.7	13.8
MDD	25,203	45.9 (12.7)	28.2		8.5	1.5		83.8	56.1	1.3	33.4	85.0	19.4
Pain Disorder	107,816	49.3 (12.2)	35.7		2.5	0.9	19.6		24.7	0.4	19.5	50.2	7.4
Other Psych Disorder	31,847	45.2 (13.6)	36.6		7.8	1.9	44.4	83.6		1.3	30.2	70.3	17.3
Schizophrenia	598	44.2 (13.2)	39.5		37.0	2.8	53.3	71.1	66.4		52.8	76.9	81.6
All	131,178	48.9 (12.9)	37.1		2.9	1.1	19.2	82.2	24.3	0.5	19.4	49.5	8.0
Gabapentin Monotherapy	57,085	50.1 (13.0)	44.2		0.4	0.4	4.8	81.5	12.8	0.1	na	na	na

Table 2

Suicide Attempt Rate per 1,000 Person Years Before and After Prescription of Gabapentin by Diagnosis Poisson Regression Model

Diagnosis	# at Risk	# Attempts Before	Rate per 1,000	# Attempts After	Rate per 1,000	ERR ²	95% CIs for ERR	P-value
Bipolar Disorder	3,783	181	47.85	119	31.46	0.62	0.41–0.94	0.026
Major Depressive Disorder	25,203	436	17.30	319	12.66	0.65	0.52–0.82	< 0.001
Schizophrenia	598	38	63.55	28	46.82	0.74	0.41–1.35	0.326
Other Psychiatric Disorder	31,847	409	12.84	323	10.14	0.69	0.55–0.88	0.002
Epilepsy	1,411	12	8.50	10	7.09	0.83	0.34–2.04	0.683
Pain Disorder	107,816	345	3.20	370	3.43	0.99	0.78–1.26	0.944
All	131,178	456	3.48	453	3.45	0.93	0.76–1.14	0.487
Gabapentin Monotherapy ¹	57,085	17	0.30	9	0.16	0.53	0.16–1.73	0.294

Note:

¹ Adjusting for concomitant diagnoses, age, and gender (subjects with any CNS drugs after index date were excluded)

² Event Rate Ratios (ERR) calculated from Poisson model with time-varying concomitant medication.