The Association between Gabapentin and Suicidality in Bipolar Patients

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Abstract

Importance: Gabapentin is an antiepileptic drug (AED) commonly used in the treatment of bipolar disorder (BPD). In 2008, the US Food and Drug Administration (FDA) concluded that it is associated with an increased risk of suicidality; however, published studies have arrived at conflicting conclusions.

Objective: To assess the association between the use of gabapentin and suicidality in a cohort of adult patients diagnosed with bipolar disorder (BPD), and to determine if the risk is greater relative to patients prescribed lithium.

Design: This is a retrospective observational study utilizing US population-based claims data assembled by PharMetrics, Inc. between 2000 and 2006.

Setting: Data were collected from US insurance claims data, and comprise patients treated in both clinical and hospital settings.

Participants: The database comprises 47,918 patients diagnosed with BPD who had two years of continuous healthcare coverage (one year before and after BPD diagnosis). Subjects were included in this analysis if they were at least 18 years old and initiated a new monotherapy prescription of either gabapentin (n=2,421) or lithium (n=3,101). For this analysis, subjects were followed for up to one year after medication initiation.

Main Outcome and Measure: Suicide attempt or self-harm (SA/SH) as defined by ICD-9 codes E950-E959.

Results: Gabapentin patients contributed 915.8 person-years (PY), while lithium patients contributed 1,421.3 PY. A total of 37 SA/SH events were identified; 21 (0.9%) in the gabapentin group and 16 (0.5%) in the lithium group (p=0.13). The unadjusted incidence rates were 22.9 and 11.3 per 1,000 PY in the gabapentin and lithium groups, respectively (p=0.03). After adjusting for concomitant medications, comorbid diagnoses, age, sex, and history of SA/SH, the hazard ratio (HR) was 2.3 (95% CI [1.2, 4.5]). Sensitivity analyses support this finding, with an adjusted HR of 1.9 (95% CI [0.9, 3.8]) among patients without a history of SA/SH, and 2.1 (95% CI [1.02, 4.5]) in a propensity score-matched analysis accounting for pre-existing illnesses and medications.

Conclusions and Relevance: The use of gabapentin is significantly associated with suicidality in patients diagnosed with bipolar disorder. Even after adjusting for significant confounders, bipolar patients treated with gabapentin have twice the risk of suicidality as compared to patients treated with lithium. Sensitivity analyses support this conclusion. Gabapentin should not be prescribed for the treatment of bipolar disorder.

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Chapter 1: Introduction, Background, and Literature Review

Bipolar Disorder

According to the DSM-IV, bipolar disorder (BPD) is a psychiatric illness characterized by manic episodes, depressive episodes, and cycles between manic and depressive states [1]. The three most common subtypes of BPD vary primarily in the presenting persistent symptom, pattern of mood disturbance, and cyclicity. Type I presents as mania and major depression, with manic polarity symptoms; Type II presents as hypomania and major depression, with depressive polarity symptoms; Type III presents as cyclothymia, with hypomania and dysthymia. It is estimated that the lifetime prevalence of BPD is between 1 and 2% in American adults [2].

The etiology of BPD is not well understood. Some hypothesize that dysregulation of gamma aminobutyric acid (GABA) system causes the disorder, based on research that shows treatments which modulate GABA, such as quetiapine and olanzapine, result in control of manic symptoms [2,3,4]. Another theory is that the disorder is caused by “kindling,” an abnormal neuronal signaling similar in nature to epileptic seizures, but occurring in non-motor areas of the brain. This theory is supported by research that shows anticonvulsant medications, such as carbamazepine and valproate, provide symptom management [2,5]. Due to these two theories, the use of anticonvulsants in the treatment of bipolar disorder has become common, with more than half of all bipolar patients being treated with anti-epileptic drugs (AEDs) [6].

Patients with BPD are at high risk for comorbid conditions such as alcoholism and drug abuse, anxiety, attention deficit hyperactivity disorder, and post-traumatic stress disorder [6]. Suicide and suicide attempts (SAs) are a major source of morbidity and mortality among bipolar patients. An estimated 60 to 80% of suicides are associated with major affective disorders, and the lifetime prevalence of suicide among bipolar patients is estimated to be 18.9% [7]. As such, symptom control and suicide prevention are key to improving health outcomes for bipolar

patients. Data on the effects of lithium in bipolar patients are voluminous, and date back to the 1970s. Baldessarini et al., performed a review of the literature and a meta-analysis in order to quantify the effects of lithium [8]. They found the crude annual rate of SA or completed suicide to be 2.6% without lithium treatment, and 0.44% with lithium treatment. The pooled analysis showed a 79.6% lower rate of SA or completed suicide while on lithium versus off. For bipolar patients, the reduction was 81.3%. Their review showed that lithium outperformed all other treatments, whether clinically or randomly assigned. The authors concluded that lithium is protective as compared to all AEDs studied, including carbamazepine, divalproex, and lamotrigine. This result is similar to that found by Guzzetta, Tondo, Centorrino, & Baldessarini, 2007, who also performed a meta-analysis and found an 88.5% reduction in suicidality when on lithium versus off [9].

Rise of AEDs as Treatment for BPD

Between 1990 and 2012, 16 AEDs were introduced to the market. Due to this increase in competition, drug manufacturers began seeking other central nervous system (CNS) disorders that could also be treated with AEDs. This, coupled with high rates of non-response to traditional mood stabilizing drugs such as lithium, led manufacturers of AEDs to target disorders such as neuropathic pain, migraine, and BPD [10].

In 1978, Ballenger and Post conducted the first study on the efficacy of the treatment of bipolar patients with an antiepileptic medication (carbamazepine) [11]. Of ten subjects studied, 7 showed a positive response with respect to mania (5), psychosis (4), and depression (2). Only 3 failed to respond. This study launched a new era in the investigation of the treatment of affective disorders, built on the theory that manic symptoms share a common etiology with epilepsy [12].

Early studies of AEDs in the treatment of BPD showed mixed results. Lamotrigine was associated with a decrease in depressive symptoms [13, 14], including in patients with

treatment-resistant BPD I/II [15]. Although lamotrigine also showed a dose-response in the treatment of depressive symptoms [16], results were inconclusive with respect to manic and hypomanic symptoms [16, 17, 18]. Topiramate has not been shown effective in the treatment of BPD-related depression [19]. However, in a study utilizing an on-off-on design, symptoms of mania were shown to decrease while subjects were on topiramate, and increase when they were off [20]. Further studies showed topiramate to be effective in the treatment of BPD-related depression whether used alone [21] or as an adjunctive treatment [19, 22].

Gabapentin was approved by the U.S. Food and Drug Administration (FDA) in 1993 as an adjunctive treatment of partial seizures, and very quickly began to be prescribed and studied for off-label purposes, including bipolar disorder, neuropathic pain, diabetic neuropathy, attention deficit disorder, migraine, and many others [23]. Studies regarding its efficacy in the treatment of bipolar disorder began appearing in the literature around 1996. Studies almost exclusively used gabapentin as an adjunctive medication for patients whose symptoms were resistant to the effects of common mood stabilizers such as lithium, carbamazepine, divalproex, and combinations of antidepressant and antipsychotic medications. Results of these studies were largely inconclusive.

In 1997, Young, Robb, Patelis-Siotis, MacDonald, & Joffe investigated the efficacy of gabapentin in the treatment of BPD-related depression. Fifteen patients with BP I or BP II were enrolled [24]. Depression was measured using the Hamilton Depression Rating Scale (HAM-D). After six weeks of treatment, a small but significant reduction in the average HAM-D score was observed, but only 53% of patients saw any improvement. In 1999, Young et al., released a second study of the efficacy of gabapentin in the treatment of BPD depression and mania [25]. Of 37 subjects enrolled, 30 presented with depression. These 30 subjects showed a significant decrease in depressive symptoms (HAM-D) within 12 weeks, and 17 maintained improvement at 6 months. They also found a significant improvement in a global assessment of functioning.

The 7 manic patients saw a significant improvement in their symptoms based on the Young Mania Rating Scale (YMRS). Adverse side effects reported included constipation, dry mouth, trouble sleeping, anxiety, blurred vision, and sexual difficulties.

In 1997, McElroy, Soutullo, Keck, & Kmetz investigated the efficacy of gabapentin for treatment-resistant manic patients [26]. This pilot trial enrolled 9 patients, 8 of whom experienced a reduction in symptoms within 3 months (scale 0-3; 0=no response or worsening of symptoms; 3=marked improvement). Of these 8 patients, 6 continued to show improved symptoms at 7 months. Altschuler et al., also found a positive response in patients enrolled in an open-label trial in 1999 [27]. Of 28 subjects enrolled, 20 (72%) saw an improvement in their symptoms as measured by the Clinical Global Impressions Scale for Bipolar Illness (CGI-BP). All of the patients with depression, mania, or hypomania (n=14) had a positive response, whereas only 56% (n=5) of those with mixed mania, and 25% (n=1) with rapid cycling saw improvement.

The first randomized placebo-controlled trials for gabapentin in the treatment of BPD began appearing in the literature around 2000. Pande, Crockatt, Janney, Werth, & Tsaroucha, 2000, conducted a study on the treatment of mania with 58 BPD patients randomized to active treatment, and 59 to a placebo [28]. Patients taking gabapentin showed no significant improvement based on the HAM-D scale, and those in the placebo arm showed a significantly greater improvement based on the YMRS. In 2000, Frye et al., performed a placebo-controlled case-crossover trial to study the effects of lamotrigine and gabapentin monotherapy on refractory BPD [14]. Thirty-one subjects were enrolled in the trial. Although the study showed a significant improvement of symptoms (CGI-BP) during treatment with lamotrigine, gabapentin was not significantly different from placebo, with approximately 20-25% of subjects experiencing a reduction in symptoms.

Although tests of efficacy were consistently mixed, gabapentin grew in popularity as a treatment for BPD, with studies reporting it to be generally well-tolerated and compatible with other mood-stabilizing medications. In 2000, gabapentin sales totaled nearly 1 billion dollars, and was primarily prescribed for off-label indications such as BPD and pain disorders [29]. In 2001, gabapentin was the second most commonly prescribed medication for BPD behind divalproex, accounting for some 21-22% of the market [29]. However, due to the fact that it was never conclusively demonstrated to be an effective treatment for BPD, gabapentin is currently only approved by the FDA for the treatment of epilepsy and post-herpetic neuralgia [29].

FDA intervention

In 2005, after growing concern that the use of AEDs increased the risk of suicidality, the FDA identified 11 AEDs for further analysis: carbamazepine, divalproex, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, and zonisamide [30]. The FDA contacted the manufacturers of these 11 medications and requested all data resulting from any parallel-arm or placebo-controlled (including low-dose placebo) with at least 30 participants be submitted for examination. Studies with ongoing blinded treatment phases were excluded from analysis. The FDA specifically requested data, including adverse events, relating to suicidality and self-harm events (completed suicide, suicide attempt, preparatory acts, suicidal ideation, self-injury, and fatal/non-fatal events lacking information).

In the FDA analysis, *suicidal behavior* was defined as completed suicide, suicide attempt, or preparatory acts. The primary endpoint of interest was defined either suicidal behavior or suicidal ideation. Secondary endpoints included suicidal behavior alone and suicidal ideation alone. For any subject experiencing multiple events, only the most serious event was considered in the analysis. Suicide-related events were identified via specified text-string searches, and were limited to those occurring while on study medication, or within one day of

discontinuing medication. Medical and statistical reviewers identified three primary indication groups: epilepsy, psychiatric (including bipolar disorder), and other (primarily pain disorders), in order to perform subgroup analyses. Drugs were considered as a whole, individually, and grouped as follows: sodium channel blocking, GABAergic or GABAmimetic, and carbonic anhydrase inhibitors. Population subgroups were also considered by age (5-17, 18-24, 25-30, 31-64, >=65), sex, race (white versus other), setting (inpatient versus outpatient), and location (North American versus not). The primary endpoint was measured in patient units and assessed via trial-stratified odds ratios. The research plan was determined a priori, including primary and secondary endpoints, populations, and subgroups of interest, and statistical analyses.

In 2008, the FDA released the results of their meta-analysis [30]. A total of 210 studies (199 placebo-controlled and 11 low-dose controlled) were identified for inclusion. Among these were 28 gabapentin placebo-controlled trials. Of the included trials, 123 (59%) were monotherapy studies. Of the 56 trials with a psychiatric indication, 86% were monotherapy. A total of 45,479 patients were included in the meta-analysis: 28,651 in active drug arms; 16,029 in placebo arms; and 799 in low-dose placebo arms. Of the 45,479 patients, 43,892 were involved in placebo-controlled trials (27,863 treatment, 16,029 placebo). There were 4,932 (11%) subjects involved in placebo-controlled studies of gabapentin (2,903 gabapentin, 2,029 placebo). Studies with a psychiatric indication comprised 11,796 (27%) patients, of whom 331 (7%) were included in placebo-controlled gabapentin trials. Among the placebo-controlled trials, there were no significant differences between the active and placebo arms with respect to age, sex, race, setting, or location.

Among the placebo-controlled trials there were 142 suicide-related events, including 4 completed suicides (104 in drug arms, and 38 in placebo arms). The overall crude odds ratio was 1.58. In the gabapentin trials, there were 2 events among the 2,903 active drug patients, and 1 event among the placebo patients, resulting in a crude odds ratio of 1.4. The overall

adjusted OR was 1.8 (95% CI [1.24, 2.66]), and for gabapentin alone was 1.57 (95% CI [0.12, 47.66]). For the secondary endpoints, the estimated adjusted OR for suicidal behavior was 2.92 (95% CI [1.44, 6.47]), and for suicidal ideation alone was 1.45 (95% CI [0.93, 2.3]). Among the trials with a psychiatric indication, there were 5.7 events per 1,000 placebo patients and 8.5 events per 1,000 drug patients, giving an estimated OR of 1.51 (95% CI [0.95, 2.45]).

The FDA ultimately found that those patients treated with AEDs had nearly twice the risk of suicidal behavior or ideation as compared to placebo (0.43% versus 0.22%) [30]. They further determined that these results were consistent among individual drugs, with 8 having ORs greater than 1. A series of sensitivity analyses confirmed these results, including a time-to-event analysis which showed an increased risk of suicidality among AED patients as early as one week after beginning treatment, and continuing through at least 24 weeks of treatment. Further, subgroup analyses did not show any patterns of increased risk, but rather that the increase was consistent across all subgroups considered.

As a result of this meta-analysis the FDA determined that all AEDs present an increased risk of suicidality, regardless of mechanism or indication, and ultimately issued safety alerts [31]. They subsequently decided that manufacturers of AEDs must include a warning in their product label regarding these increased risks, as well as develop Medication Guides to assist patients with understanding these risks [32].

Follow-Up Research

The FDA report and resulting action (requiring additional warnings) led to heated debate among academic researchers regarding the potential harms associated with the use of AEDs, with many authors critical of the FDA methodology and use of what many considered to be limited data [33]. Hesdorffer and Kanner argued that the meta-analysis performed by the FDA is flawed for three reasons [34]. First, the FDA relied upon adverse event data rather than systematically

collected data. Second, the FDA grouped all AEDs by their anti-epileptic effect, ignoring the variation in mechanism. Hesdorffer and Kanner maintain that this second issue is substantiated by the variation in the relative risks of the individual medications, although the FDA considered the individual effects to be consistent. Third, the risk caused by untreated epilepsy is greater than the risk of suicidality among epileptic patients. Regarding the safety of AED use in bipolar patients, Hesdorffer and Kanner suggest that data are lacking and more research must be undertaken.

In 2014, Ferrer et al., completed a systematic review of studies involving AEDs and the risk of suicide [35]. Among their complaints about the FDA study was that the meta-analysis presented potential selection bias, bias in adverse event ascertainment, confounding by previous suicidality, and potential heterogeneity. Gibbons, Hur, Brown, & Mann, 2010, echoed these concerns in their 2010 paper [36]. They note that the FDA study required the exclusion of any study with zero events, and point out that for gabapentin in particular, this reduced the number of viable trials from 49 to 3.

Following the publication of the FDA's meta-analysis and subsequent determination that AED manufacturers must include a warning regarding the increased risk of suicidality, many researchers set out to investigate the association between AED use and suicidality. Because AEDs as a class had been determined to increase suicidality, ethical considerations precluded the use of randomized controlled trials, and researchers involved in this wave of study relied on observational studies of large, claims-based data sets for their analyses.

Patorno et al., used a proportional hazards model to evaluate the risk of suicide attempt or self-harm (SA/SH), completed suicide, or violent death for patients on antiepileptic medications as compared to a reference treatment [37]. A total of 130,698 patients using gabapentin contributed 142,865 treatment episodes. These were compared to 52,127 patients using topiramate who

contributed 57,853 treatment episodes. The model, adjusted for age, sex, year, extensive comorbidities, and concomitant medication, showed an increased risk of suicidality with a hazard ratio of 1.44 (95% CI [1.13-1.83]). A sub-analysis showed that among patients with a diagnosed mood disorder the adjusted hazard ratio was 2.0 (95% CI [1.43-2.79]). Further, this study showed a significantly increased risk within the first 14 days of treatment, suggesting that AEDs may cause adverse behavioral changes before the therapeutic effects manifest.

Collins and McFarland studied 12,662 Oregon Medicaid patients diagnosed with bipolar disorder [38]. A Cox proportional hazards model was used to compare completed suicide or emergency department visit due to a SA/SH between patients treated with AEDs to those treated with lithium. Lithium had the lowest completed suicide rate in the study, whereas gabapentin had the highest. Patients treated with lithium had a rate of 0.78 completed suicides and 5.86 SAs per 1,000 person-years. Patients treated with gabapentin had a rate of 3.5 completed suicides and 9.49 SAs per 1,000 person-years. The proportional hazards model adjusted for comorbid physical and mental illness, as well as concomitant use of antidepressants, antipsychotics, age, sex, and year of diagnosis. The adjusted hazard ratio for SA/SH was 1.6 ($p = 0.2$), and for completed suicide was 2.6 ($p < 0.001$).

Pugh et al., 2012, studied the association between AED use and suicide-related events in a cohort of older bipolar veterans [39]. Suicide-related events were measured using ICD-9 codes, and analysis was limited to new prescriptions (no other AED use in the year prior to the index prescription). Using a propensity score adjusted Cox proportional hazards model (to account for confounding caused by the likelihood of being prescribed an AED), they found that, relative to patients with no AED exposure, those taking any AED had an increased risk of suicidality (HR=3.9, 95% CI [2.93, 5.19]), and patients taking only gabapentin also had an increased risk (HR = 2.56, 95% CI [1.96-4.16]).

Gibbons, Hur, Brown, and Mann have produced two studies on the association between SA and gabapentin. The first study analyzed 131,178 patients treated with gabapentin for SAs before and after beginning medication [36]. Of these, there were 3,783 bipolar patients. Overall they found a rate of 3.48 per 1,000 person-years before beginning medication and 3.45 per 1,000 person-years after beginning medication. A model which adjusted for comorbid pain diagnosis and concomitant anticonvulsant, antidepressant, antipsychotic, or lithium use found a rate ratio of 0.62 ($p = 0.026$), indicating that gabapentin provides a protective effective against suicidality.

The second study examined the association between SA and monotherapy for the 11 AEDs examined by the FDA [40]. The study utilized a database of 47,918 bipolar patients. Patients were classified by monotherapy with one of the 11 AEDs, lithium therapy, or no therapy. Overall, the authors report no difference between SA rates in patients treated with AEDs (13 per 1,000 person-years) versus those not treated with an AED or lithium (13 per 1,000 person-years). For patients treated with gabapentin, the authors report that prior to treatment the rate of SA was 61 per 1,000 person-years, versus 13 per 1,000 person-years after treatment, again showing a protective effect.

Patorno, 2010, noted several potential flaws with the analyses presented by Gibbons et al. [41]. Chief among these is that the cohorts eliminate completed suicide by design, as the subjects are required to have a full year of continuous medical coverage after their initial bipolar diagnosis or their initial gabapentin prescription. Also of concern is that the analysis suffers from immortal time bias, and that the protective effect shown is a result of an increase in suicidal activity that occurs prior to treatment [42]. Ferrer et al., also noted potential problems, including exposure misclassification, potential selection bias, potential outcome misclassification, confounding by indication, and conflict of interest [35].

Current Study

Due to the ongoing, contradictory nature of published research presenting results that support both harmful and protective effects of gabapentin with respect to suicidality in the treatment of BPD, the general consensus is that more research is necessary [43]. Bearing in mind the criticisms published regarding the methods utilized in the Gibbons studies [36, 40], the purpose of our analysis is to reexamine the data presented in this research group's cohort analyses of bipolar patients. Our study will endeavor to employ statistical techniques to arrive at a more accurate, less biased understanding of the association between suicidality and the gabapentin in the BPD population. Our methodology will include the identification of patients with novel, monotherapy gabapentin and lithium prescriptions, which will allow us to isolate the effects of individual treatments. We will compare gabapentin to lithium, considered the gold standard treatment for BPD, in order to mitigate confounding by indication (severity of illness). Our study will control for concomitant medications (anticonvulsants, antidepressants, and antipsychotics), and more comorbid conditions (cancer, HIV, pain disorder, epilepsy, schizophrenia, major depressive disorder, and other psychological disorders), as well as a documented history of suicidality or self-harm. We will use a time-to-event analysis, with follow up time beginning the day a new prescription is filled, and ending with the occurrence of an SA/SH event, or with switching/discontinuing medication. This will help prevent exposure classification bias and immortal time bias. Finally, we will conduct two sensitivity analyses (including a propensity-score matched analysis) in order to verify the robustness of our results.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: American Psychiatric Association; 1994. A text revision of DSM-IV was published in 2000 as Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, abbreviated DSM-IV-TR.

2. McCabe S. Advances in the Pharmacological Treatment of Bipolar Affective Disorders. *Perspectives in Psychiatric Care*. 2003; 39(3):95-103.

3. Delbello MP, Schwiers ML, Rosenberg HL, Strakowski SM. A double-blind, randomized, placebo-controlled study of quetiapine as adjunctive treatment for adolescent mania. *Journal of the American Academy of Child and Adolescent Psychiatry.* 2002; 41:1216-1223.

4. Tohen M, Sanger TM, McElroy SL. Olanzapine versus placebo in the treatment of acute mania. *American Journal of Psychiatry.* 1999; 156:702-709.

5. Dunn RT, Frye M, Kimbrell TA, Denicoff KD, Leverich GS, Post RM. The efficacy and use of anticonvulsants in mood disorders. *Clinical Neuropharmacology.* 1998; 21:215-235.

6. National Institutes of Mental Health. Bipolar disorder in adults. *U.S. Department of Health and Human Services*. 2012.

7. Goodwin FK. Anticonvulsant therapy and suicide risk in affective disorders. *Journal of Clinical Psychiatry*. 1999;60 Suppl 2:89-93; discussion 111-116.

8. Baldessarini RJ, Tondo L, Davis P, Pompili M, Goodwin FK, Hennen J. Decreased risk of suicides and attempts during long-term lithium treatment: a meta-analytic review. *Bipolar Disorders*. 2006; 8(5 Pt 2):625-39.

9. Guzzetta F, Tondo L, Centorrino F, Baldessarini RJ. Lithium treatment reduces suicide risk in recurrent major depressive disorder. *Journal of Clinical Psychiatry.* 2007; 68(3):380-383.

10. Bialer, M. Why are antiepileptic drugs used for nonepileptic condition? *Epilepsia*. 2012; 53(7):26-33.

11. Ballenger JC, Post RM. Therapeutic effects of carbamazepine in affective illness: A preliminary report. *Communications in Psychopharmacology*. 1978; 2(2):159-175.
12. Macdonald KJ, Young LT. Newer antiepileptic drugs in BPD: rationale for use and role in therapy. *CNS Drugs*. 2002; 16:549-562.
13. Calabrese JR, Fatemi SH, Woyshville MJ. Antidepressant effects of lamotrigine in rapid cycling bipolar disorder [letter]. *American Journal of Psychiatry.* 1996; 153(9):1236.
14. Frye MA, Ketter TA, Kimbrell TA, Dunn RT, Speer AM, Osuch EA, Luckenbaugh DA, Cora-Locatelli G, Leverich GS, Post RM. A placebo-controlled study of lamotrigine and gabapentin monotherapy in refractory mood disorders. *Journal of Clinical Psychopharmacology*. 2000; 20(6):607-614.
15. Sporn J, Sachs G. The anticonvulsant lamotrigine in treatment resistant manic-depressive illness. *Journal of Clinical Psychopharmacology.* 1997; 17(3):185-189.
16. Calabrese JR, Bowden CL, Sachs GS, Asscher JA, Monaghan E, Rudd GD. A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. *Journal of Clinical Psychiatry*. 1999; 60(2):79-88.
17. Calabrese JR, Bowden CL, McElroy SL, Cookson J, Andersen J, Keck Jr. PE, Rhodes L, Bolden-Watson C, Zhou J, Ascher JA. Spectrum of activity of lamotrigine in treatment-refractory bipolar disorder. *American Journal of Psychiatry.* 1999; 156(7):1019-1023.
18. Berk M. Lamotrigine and the treatment of mania in bipolar disorder. *European Neuropsychopharmacology*. 1999; 9 Suppl. 4:S119-23.

19. McElroy SL, Suppes T, Keck Jr PE, Frye MA, Denicoff KD, Altshuler LL, Brown ES, Nolen WA, Kupka RW, Rochussen J, Leverich GS, Post RM. Open-label adjunctive topiramate in the treatment of bipolar disorders. *Biological Psychiatry*. 2000; 47:1025-1033.
20. Grunze HCR, Normann C, Langosch J, Sterr AB, Schloesser S, Kleindienst N, Walden J. Antimanic efficacy of topiramate in 11 patients in an open trial with on-off-on design. *Journal of Clinical Psychiatry*. 2001; 62(6):464-468.
21. Calabrese JR, Keck PE, McElroy SL, Melvin S. Pilot study of topiramate as monotherapy in the treatment of acute mania. *Journal of Clinical Psychopharmacology*. 2001; 21(3):340-342.
22. Chengappa KNR, Rathore D, Levine J, Atzert R, Solai L, Parepally H, Levin H, Moffa N, Delaney J, Brar JS. Topiramate as add-on treatment for patients with bipolar mania. *Bipolar Disorders*. 1999; 1:42-53.
23. Mack A. Examination of the evidence for off-label use of gabapentin. *Journal of Managed Care Pharmacy.* 2003; 9(6):559-568.
24. Young LT, Robb JC, Patelis-Siotis I, MacDonald C, Joffe RT. Acute treatment of bipolar depression with gabapentin. *Biological Psychiatry*. 1997; 42:851-853.
25. Young LT, Robb JC, Hasey GM, MacQueen GM, Patelis-Siotis I, Marriott M, Joffe RT. Gabapentin as an adjunctive treatment in bipolar disorder. *Journal of Affective Disorders*. 1999; 55:73-77.
26. McElroy SL, Soutullo CA, Keck PE, Kmetz GF. A pilot trial of adjunctive gabapentin in the treatment of bipolar disorder. *Annals of Clinical Psychiatry*. 1997; 9(2):99-103.
27. Altschuler LL, Keck PE, McElroy SL, Suppes T, Brown ES, Denicoff K, Frye M, Gitlin M, Hawng S, Goodman R, Leverich G, Nolen W, Kupka R, Post R. Gabapentin in the acute treatment of refractory bipolar disorder. *Bipolar Disorders*. 1999; 1:61-65.

28. Pande AC, Crockatt JG, Janney CA, Werth JL, Tsaroucha G. Gabapentin in bipolar disorder: a placebo-controlled trial of adjunctive therapy. *Bipolar Disorders*. 2000; 2:249-255.
29. Chace MJ, Zhang F, Fullerton CA, Huskamp HA, Gilden D, Soumerai SB. Intended and unintended consequences of the gabapentin off-label marketing lawsuit among patients with bipolar disorder. *Journal of Clinical Psychiatry.* 2012; 73(11):1388-1394.
30. Food and Drug Administration. Statistical review and evaluation: Antiepileptic drugs and suicidality. *U.S. Department of Health and Human Services*. 2008.
31. Food and Drug Administration. FDA Requires Warnings about Risk of Suicidal Thoughts and Behavior for Antiepileptic Medications. 2008. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm100197.htm
32. Food and Drug Administration. Suicidal behavior and ideation and antiepileptic drugs. 2009. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm100190.htm
33. Avorn J. Drug warnings that can cause fits – communicating risks in a data-poor environment. *New England Journal of Medicine.* 2008; 359:991-994.
34. Hesdorffer DC, Kanner AM. The FDA alert on suicidality and antiepileptic drugs: Fire or false alarm? *Epilepsia*. 2009; 50(5):978-86.
35. Ferrer P, Ballain E, Sabate M, Vidal X, Rottenkolber M, Amelio J, Hasford J, Schmiedl S, Ibanez L. *Neuroepidemiology*. 2014; 42:107-120.
36. Gibbons RD, Hur K, Brown CH, Mann JJ. Gabapentin and suicide attempts. *Pharmacoepidemiology and Drug Safety*. 2010; 19(12):1241-7.

37. Patorno E, Bohn RL, Wahl PM, Avorn J, Patrick AR, Liu J, Schneeweiss S. Anticonvulsant medications and the risk of suicide, attempted suicide, or violent death. *JAMA.* 2010; 303(14):1401-1409.

38. Collins JC, McFarland BH. Divalproex, lithium and suicide among Medicaid patients with bipolar disorder. *Journal of Affective Disorders*. 2008; 107(1-3):23-28.

39. Pugh MJV, Copeland LA, Zeber JE, Wang CH, Amuan ME, Mortensen EM, Tabares JV, Van Cott AC, Cooper TL, Cramer JA. Antiepileptic drug monotherapy exposure and suicide-related behavior in older veterans. *Journal of the American Geriatrics Society*. 2012; 60(11):2042-2047.

40. Gibbons RD, Hur K, Brown CH, Mann JJ. Relationship between antiepileptic drugs and suicide attempts in patients with bipolar disorder. *Archives of General Psychiatry*. 2009; 66(12):1354-1360.

41. Patorno, E. Letters: Antiepileptic Medications and the Risk of Suicide. *JAMA.* 2010; 304(5):522-523.

42. Suissa S. Immortal Time Bias in Pharmaco-epidemiology. *American Journal of Epidemiology*. 2008; 167(4):492-499.

43. Hesdorffer DC, Berg AT, Kanner AM. An update on antiepileptic drugs and suicide: Are there definitive answers yet? *Epilepsy Currents*. 2010; 10(60:137-145.

Chapter 2: Current Study

Introduction and Background

The Food and Drug Administration (FDA) approved gabapentin in 1993 as an adjunctive treatment of partial seizures. It quickly began to be prescribed and studied for off-label purposes, including bipolar disorder (BPD), neuropathic pain, diabetic neuropathy, attention deficit disorder, migraine, and many others [1]. Studies regarding gabapentin's efficacy in the treatment of BPD began appearing in the literature around 1996. Although they consistently showed mixed results, gabapentin grew in popularity as a treatment for BPD. In 2000, gabapentin sales totaled nearly 1 billion dollars, and it was prescribed primarily for off-label indications such as BPD and pain disorders [2]. In 2001, gabapentin was the second most commonly prescribed medication for BPD behind divalproex, accounting for some 21-22% of the market [3]. Gabapentin, however, is currently only approved for the treatment of epilepsy and post-herpetic neuralgia, as it was never conclusively demonstrated to be an effective treatment for BPD [3].

In 2005, after growing concern that antiepileptic drugs (AEDs) increased the risk of suicidality, the FDA identified 11 AEDs for further analysis: carbamazepine, divalproex, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, and zonisamide [3]. In 2008, the results of the meta-analysis were released [3]. The FDA ultimately found that patients treated with AEDs had nearly twice the risk of suicidal behavior or ideation as compared to placebo (0.43% versus 0.22%), and reported a stratified, adjusted OR of 1.8 (95% CI [1.24, 2.66]). They further determined that these results were consistent among individual drugs, and across all subgroups studied. Among the trials with a psychiatric indication, there were 5.7 events per 1,000 placebo patients and 8.5 events per 1,000 drug patients, giving an estimated OR of 1.51 (95% CI [0.95, 2.45]). In the gabapentin trials, there

were 2 events among the 2,903 active drug patients, and 1 event among the placebo patients, resulting in a crude odds ratio of 1.4. The adjusted OR for gabapentin alone was 1.57 (95% CI [0.12, 47.66]).

As a result of this meta-analysis the FDA determined that all AEDs present an increased risk of suicidality, regardless of mechanism or indication. They ultimately issued safety alerts and decided that manufacturers of AEDs must include a warning in their product label and develop Medication Guides to assist patients with understanding these risks [4]. These results led to strong criticism of the FDA's methodology, including the possibility that the results were affected by selection bias, bias in adverse event ascertainment, confounding by previous suicidality, and potential heterogeneity in treatment mechanism [5,6]. Gibbons, Hur, Brown, & Mann, 2010 echoed these concerns, noting that the FDA study required the exclusion of any study with zero events, and pointed out that for gabapentin in particular, this reduced the number of viable trials from 49 to 3 [7].

In the wake of these criticisms, many researchers set to the task of investigating the association between AED use and suicidality. Patorno et al., 2010, used a proportional hazards (PH) model to evaluate the risk of suicide attempt or self-harm (SA/SH), completed suicide, or violent death for patients on AEDs as compared to a reference treatment [8]. Their model, adjusted for age, sex, year, extensive comorbidities, and concomitant medication, showed an increased risk of suicidality with a hazard ratio of 1.44 (95% CI [1.13-1.83]). A sub-analysis showed that among patients with a diagnosed mood disorder the adjusted hazard ratio was 2.0 (95% CI [1.43-2.79]).

Collins and McFarland studied 12,662 Oregon Medicaid patients diagnosed with BPD [9]. A Cox PH model was used to compare completed suicide or emergency department visit due to a SA/SH between patients treated with AEDs to those treated with lithium. The PH model adjusted for comorbid physical and mental illness, concomitant use of antidepressants, antipsychotics,

age, sex, and year of diagnosis. Gabapentin had an adjusted hazard ratio of 1.6 ($p = 0.2$) for SA/SH, and 2.6 ($p < 0.001$) for completed suicide.

Pugh, et al., 2012, studied the association between AED use and suicide-related events in a cohort of older bipolar veterans [10]. Suicide-related events were measured using ICD-9 codes, and analysis was limited to new prescriptions (i.e., no other AED use in the year prior to the index prescription). A propensity score-adjusted Cox PH model showed that, relative to patients with no AED exposure, patients taking any AED had an increased risk of suicidality (HR=3.9, 95% CI [2.93, 5.19]), and those patients taking only gabapentin also had an increased risk (HR = 2.56, 95% CI [1.96-4.16]).

Gibbons, Hur, Brown, & Mann, 2009, examined the association between SA and monotherapy for the 11 AEDs examined by the FDA [11]. The study utilized a database of 47,918 bipolar patients who were classified by monotherapy with one of the 11 AEDs, lithium therapy, or no therapy. Overall, the authors report no difference between SA rates in patients treated with AEDs (13 per 1,000 person-years) versus those not treated with an AED or lithium (13 per 1,000 person-years). For patients treated with gabapentin, the authors report that prior to treatment the rate of SA was 61 per 1,000 person-years, versus 13 per 1,000 person-years after treatment, again showing a protective effect.

Patorno, 2010, noted several potential flaws with the analysis presented by Gibbons et al., 2009 [12]. Chief among these was that the design eliminated completed suicides in the cohorts, as the subjects were required to have a full year of continuous medical coverage after their initial bipolar diagnosis or their initial gabapentin prescription. Also of concern was that the analyses suffered from immortal time bias, and that the protective effect shown was a result of an increase in suicidal activity that occurred prior to treatment [12]. Ferrer et al., 2014, also noted potential problems, including exposure misclassification, potential selection bias, potential

outcome misclassification, confounding by indication, and conflict of interest [6].

The above-mentioned studies present a conflicting image regarding the effects of gabapentin with respect to suicidality in the treatment of BPD, and support the need for more research. In this study we will reexamine the data presented in the Gibbons bipolar cohort analyses in order to arrive at a more accurate, less biased understanding of the association between suicidality and gabapentin exposure in the BPD population. In order to mitigate confounding by indication (severity of illness) we will compare gabapentin to lithium. Our study will control for concomitant medications (anticonvulsants, antidepressants, and antipsychotics), and more comorbid conditions (cancer, HIV, pain disorder, epilepsy, schizophrenia, major depressive disorder, and other psychological disorders), as well as a documented history of suicidality or self-harm. We will prevent exposure classification and immortal time bias by using a time-to-event analysis, with follow up time beginning the day a new prescription is filled, and ending with the occurrence of an SA/SH event, or with switching/discontinuing medication. Finally, we will conduct two sensitivity analyses (including a propensity score-matched analysis) in order to verify the robustness of our results.

Methods

Data Source

Data for this study came from the PharMetrics Patient Centered Database. The data set was originally compiled by PharMetrics, Inc. for the Gibbons' bipolar cohort study [11] and was acquired by the current authors (WL, MF) during the discovery process in a lawsuit against Pfizer, in which Gibbons provided expert witness testimony. The data comprise 47,918 bipolar patients that were drawn from medical claims between 2000 and 2006. In order to have been included in the data set, patients were required to be continuously enrolled in the same health care plan for one year both before and after their bipolar diagnosis. The data set includes

demographics (age, sex), date of bipolar diagnosis, pharmaceutical records including dates for prescriptions of lithium and AEDs, as well as concomitant medications (antipsychotics, antidepressants, and anticonvulsants), comorbid diagnoses, and dates of SA/SH.

Study Cohort

For the current study, we identified all patients who began a new prescription of gabapentin or lithium. Lithium was chosen as the comparison medication as it is considered the standard of care for BPD. From the date of the initial prescription, subjects were followed for up to one year for one of the following outcomes: SA/SH (defined by ICD-9 codes E950-E959) (Table 1); addition of another AED (Table 2); switching between lithium and gabapentin; or discontinuation of the prescription as defined by a gap of more than 30 days between the end of one prescription period and the beginning of a new prescription. The exposure risk window was extended by 30 days from the end of the last lithium or gabapentin prescription period for any subject censored due to medication discontinuation. Any subject with an SA/SH event or concomitant AED prescription on the same day as beginning the initial treatment prescription, or under the age of 18 was excluded from the analysis.

Statistical Analysis Plan

The gabapentin and lithium treatment groups were assessed for number of SA/SH events and total person-years (PY). Comorbid conditions considered included a diagnosis of cancer, HIV, pain disorder, epilepsy, schizophrenia, major depressive disorder, and other psychological disorders (including drug and alcohol abuse) (Table 3). Other potential confounders included concomitant medications (antipsychotics, antidepressants, and anticonvulsants, as identified by the National Drug Code directory), age, sex, and prior SA/SH diagnosis (any diagnosis prior to the index prescription). Concomitant medications and comorbid diseases were classified in two ways: existing prior to the index prescription, or concurrent with the study period. In order to be

considered a pre-existing prescription, the medication period (prescription date plus days-supply) had to include the index date. Any pre-existing medication, as well as any medication prescribed during the study period, was considered concurrent. Any comorbid disease diagnosed prior to the index date was considered a pre-existing and concurrent condition, whereas any diagnosis during the study period was considered concurrent only. Incidence of SA/SH was evaluated with Fisher's exact test, and incidence rates were evaluated by Poisson regression with a log-time offset. Potential confounding variables were investigated using Fisher's exact test for categorical variables and t-tests for continuous variables. Crude and adjusted hazard rates were evaluated with a Cox PH model.

In addition to the above primary analysis, two sensitivity analyses were conducted. First, due to the increased risk of suicidality and potential treatment bias resulting from a subject's history of SA/SH, we used the previously detailed methods to examine the association between gabapentin and suicidality in patients without a history of SA/SH (any incident prior to the index prescription). Second, in order to mediate any differences between the gabapentin and lithium groups, we conducted a propensity score matched (PSM) analysis. We first used a stepwise logistic regression model to estimate the probability of receiving either gabapentin or lithium based on pre-existing conditions and prescriptions for each subject in the study. Gabapentin subjects were then matched to lithium subjects using the Greedy-5 algorithm as described by Parsons [14]. We then analyzed the propensity matched data with the above detailed methods. All analyses were performed using SAS 9.4. This study was approved by the Oregon Health & Science University (OHSU) Institutional Review Board (IRB00012073).

Results

We identified a total of 5,522 patients who initiated a new prescription for either gabapentin or lithium (Figure 1). Of these, 2,421 (43.8%) were treated with gabapentin, and 3,101 (56.2%) were treated with lithium (Table 4). On average, gabapentin patients were older (43.5 versus 40.6, p<0.0001), and more likely to be female (67.3% versus 58.7%, p<0.0001). Gabapentin patients were significantly more likely to have comorbid epilepsy, pain disorder, major depressive disorder, other psychological disorders, and HIV, whereas lithium patients were more likely to have comorbid schizophrenia. Accordingly, gabapentin patients were more likely to have a concomitant prescription for antidepressants (78.9% versus 61.2%, p=0.0001), and anticonvulsants (18.7% versus 14%, p<0.0001), and lithium patients were more likely to have concomitant antipsychotics (35.4% versus 27.9%, p<0.0001). There was no significant difference in the risk of prior SA/SH attempt (1.3% among gabapentin users versus 1.4% among lithium users, p=0.82).

Study subjects contributed a total of 2,337.1 person-years to the analysis (Table 5). The gabapentin cohort contributed 915.8 PYs versus 1,421.3 PY in the lithium cohort. On average, gabapentin patients had 138.1 days of follow up time, compared to 167.3 days for lithium patients (p<0.0001). There were a total of 37 SA/SH events, 21 (56.8%) in the gabapentin group and 16 (43.2%) in the lithium group (p=0.13). This resulted in an unadjusted incidence rate of 22.9 per 1,000 PY in the gabapentin cohort versus 11.3 per 1,000 PY in the lithium cohort (p=0.03). The crude PH ratio was 1.96 (95% CI [1.02, 3.76]). A Cox PH model was fit with all concurrent covariates of interest, with the exception of diagnoses for HIV, cancer, and epilepsy, because of collinearity. The resulting model showed an adjusted hazard rate of 2.1 (95% CI [1.1, 4.2]). We then used stepwise regression (entry p=0.20, exit p=0.05) in order to assess the association with the most parsimonious model. This resulted in a Cox PH model that included

treatment group, age, prior SA/SH, and concurrent diagnosis of other psychological disorders. The adjusted hazard ratio was 2.3 (95% CI [1.2, 4.5]).

Sensitivity Analyses

I. Patients without a history of SA/SH event

There was a total of 76 subjects with a history of SA/SH events prior to their index prescription. Of these, 32 (42.1%) were in the gabapentin group, and 44 (57.9%) were in the lithium group. Excluding these patients did not significantly change the observed distribution of patient characteristics (Table 6). Gabapentin users continued to be significantly older and female, with greater prevalence of concurrent epilepsy, pain disorder, major depressive and other psychological disorders, HIV, and concurrent use of antidepressants and anticonvulsants. Lithium users were significantly more likely to have comorbid schizophrenia and to use antipsychotics. There was no significant difference in cancer rates.

Study subjects without a history of SA/SH contributed a total of 2,315.5 person-years, with an average of 138.8 and 168 days of follow up in the gabapentin and lithium groups respectively ($p<0.0001$) (Table 7). During follow up, there was a total of 33 SA/SH events, with 18 (54.5%) among gabapentin users, and 15 (45.5%) among lithium users ($p=0.22$). This resulted in crude rates of 19.8 and 10.7 SA/SH events per 1,000 PY in the gabapentin and lithium groups respectively ($p=0.08$). The crude hazard ratio was 1.8 (95% CI [0.9, 3.6]). We fit a Cox PH model, again with all concurrent covariates of interest except HIV, epilepsy and schizophrenia. The adjusted hazard ratio was 1.87 (95% CI [0.9, 3.8]). Using stepwise selection as detailed above, the resulting model included age, major depressive disorder, and other psychological disorders, but did not include treatment group.

II. Propensity Score-Matched Analysis

For this analysis we first fit a logistic regression model including all of the pre-existing comorbid conditions and pre-existing medications, and used stepwise selection (entry p=0.20, exit p=0.05) to estimate the probability for each subject having been prescribed gabapentin. The final model included age, sex, pre-existing use of antidepressants and anticonvulsants, and prior diagnoses of pain disorder, other psychological disorders, HIV, and cancer. We were able to match 2,079 lithium patients to 2,079 gabapentin patients, retaining 85.9% of our original gabapentin subjects, but only 67% of our original lithium patients. After matching, there were no significant differences between the two groups with respect to age, sex, prior SA/SH events, or any pre-existing medication or comorbidity (Table 8). Additionally, there were no significant differences with respect to concurrent epilepsy, schizophrenia, HIV, cancer, or use of anticonvulsants. However, the groups remained significantly different with respect to concurrent diagnoses of pain, major depressive, and other psychological disorders, and use of antidepressants and antipsychotics (Table 9).

These 4,158 subjects contributed a total of 1,753.8 person-years, with an average of 139.5 and 168.5 days for the gabapentin and lithium groups respectively (p<0.0001) (Table 10). There were a total of 31 SA/SH events during follow up: 20 (64.5%) in the gabapentin group, and 11 (35.5%) in the lithium group (p=0.15). The crude SA/SH rates were 25.2 per 1,000 PY for gabapentin and 11.5 per 1,000 PY for lithium (p=0.04). The crude hazard ratio was 2.1 (95% CI [1.01, 4.41]). After adjusting for all concurrent medications and comorbid diagnoses (with the exception of HIV which was collinear with other covariates), the resulting hazard ratio was 2.1 (95% CI [0.98, 4.4]). Applying stepwise selection (entry p=0.20, exit p=0.05), the most parsimonious model included medication group, age, prior SA/SH, and comorbid diagnoses of major mood and other psychological disorders. The resulting hazard ratio was 2.1 (95% CI [1.02, 4.5]).

Discussion

Conclusions

We reexamined the Gibbons cohort of patients diagnosed with BPD and we focused our attention on BPD patients who initiated a new prescription of either gabapentin or lithium. Our analysis demonstrated a statistically significant association between the use of gabapentin and the risk of suicidality and self-harm. Specifically, we have shown that, even after adjusting for demographics, comorbid diagnoses, concomitant medications, and a history of SA/SH, bipolar patients treated with gabapentin have approximately twice the risk of SA/SH as compared to patients treated with lithium (HR=2.3; 95% CI [1.2, 4.5]). Further, sensitivity analyses, including propensity score matching, support this conclusion.

Using this same data set, Gibbons et al., 2009, found no significant increase in suicidality among bipolar patients when comparing pre-treatment rates to post-treatment rates among those who initiate a gabapentin prescription [11]. Further, their results even suggest that gabapentin is protective, with a reported event rate ratio of 0.15 (95% CI [0.05, 0.47]). However, the Gibbons studies received heavy criticism for data and analysis flaws, as well as raising significant concerns about potential conflict of interest given that the data and analyses were paid for by Pfizer in conjunction with pending litigation for which Gibbons would provide expert witness testimony [6,12].

Our analysis provides contrasting findings to those of Gibbons and adds to the body of literature in support of the hypothesis that gabapentin does in fact increase suicidality in bipolar patients, suggesting a doubling of the risk of SA/SH.

Limitations

Our analysis is limited by fundamental, irreconcilable problems with the data set. First, because the data set was constructed specifically for the Gibbons study, we were limited by their inclusion criteria, which restricted data to patients with two uninterrupted years of health insurance coverage. There is no way to account for the outcomes of those patients who lost coverage. More importantly, we cannot speak to rates of completed suicide, as any completed suicide would have been excluded by the "continuous insurance coverage" definition. We note, however, that this likely results in an underestimation of the true effect of gabapentin, due to the fact that a history of suicidality is the strongest predictor of future completed suicide. Therefore, we expect that the increase in SA/SH observed here would translate into a greater rate of completed suicide among patients taking gabapentin. The Gibbons study also dictated which concomitant medications were to be included and we could not account for anything other than antidepressants, anticonvulsants, and antipsychotics. Though we would have preferred to control for more concomitant medications (i.e., pain medications and benzodiazepines), it is likely that these are correlated with the comorbid conditions for which we accounted.

Second, because this was an observational study of insurance claims data, we have no way of measuring the severity of illness. We attempted to mitigate this constraint by using a comparably medicated control group. Third, we have no way of accounting for any nonmedical treatments, such as psychotherapy, though there is no reason to believe that such treatments would be differentially distributed. Fourth, patients were not randomized to the treatment groups, and therefore differences in SA/SH rates may be due to other, unmeasured differences between those who were prescribed gabapentin and those who were prescribed lithium. However, due to correlations between known and unknown confounding conditions and medications, our use of the propensity score-matched analysis likely had the added benefit of balancing the groups with respect to these unknown confounders. Fifth, we cannot be certain of patient adherence to the

medication, though our definition of “continuous use” minimizes the amount of potentially misclassified study time. Finally, because the data were drawn from insurance claims, there may be non-differential reporting of comorbid illnesses. For instance, it is plausible that a subject may have had a cancer diagnosis prior to the study period, but it was not noted again until after their index prescription. Thus the patient would be noted to have a concurrent cancer diagnosis, but not a pre-existing diagnosis. However, there is no reason to believe that this would disproportionately affect one arm over the other.

Strengths

Despite these limitations, we feel this study presents an accurate, rigorous examination of the data available. In so far as statistical methods allow, we attempted to mediate the potential impact of the above-mentioned shortcomings of the data. There are many strengths to our study. Chief among these is that we examined patients who initiated a new, monotherapy prescription for gabapentin or lithium. Thus we were able to isolate the potential effects of each medication. This is of particular concern, given the fact that the FDA has determined that AEDs as a class increase suicidality. Our conclusions regarding gabapentin are therefore insulated from the potential effects of other AEDs. Second, our use of Cox PH models accurately accounts for actual exposure time. Third, our models accounted for many comorbid conditions and concomitant medications, as well as a history of suicidality. Finally, and perhaps most importantly, we measured events from the index prescription date, rather than comparing SA/SH events prior to medication to those following medication, which likely produces misleading results due to the increase in suicidal behaviors in the months preceding initial medication (and in the case of the Gibbons study, results in a protective effect for gabapentin). Our sensitivity analyses further evaluated the effect of these potential confounders, and our results remained consistent.

Public Health Implications

The legal and public health implications involved in this matter are complex and have profound consequences. Patients with BPD have a right to effective *and safe* treatment. Considering it has never been proved effective in controlling BPD symptoms, and has been specifically noted as not effective and not recommended by leading experts, we may question why gabapentin continues to be used as a treatment for BPD at all. Patients with BPD have significantly higher risk of suicidality and completed suicide, with approximately 25-50% of patients with BPD attempting suicide in their lifetime. The annual rate of completed suicide in the bipolar population is 1%; more than 66 times greater than the rate in the general population (estimate 0.015%) [15]. It is imperative that we not exacerbate the situation via use of medications that can induce suicidality.

Along with the existing body of literature, we hope that this study will steer clinicians away from prescribing gabapentin to bipolar patients. Additionally, we suggest that clinicians adopt thorough mental health screening practices when considering prescribing gabapentin to patients with diagnoses of epilepsy or pain, two conditions that are strongly associated with depression and mood disturbances. We feel the evidence strongly supports that gabapentin increases the risk of suicidality in BPD patients. However, for the FDA approved indications, the risks associated with not receiving treatment may outweigh the risks associated with gabapentin [16]. Therefore, it is of the upmost importance to monitor any patient taking gabapentin.

Figure 1. Study Cohort Selection

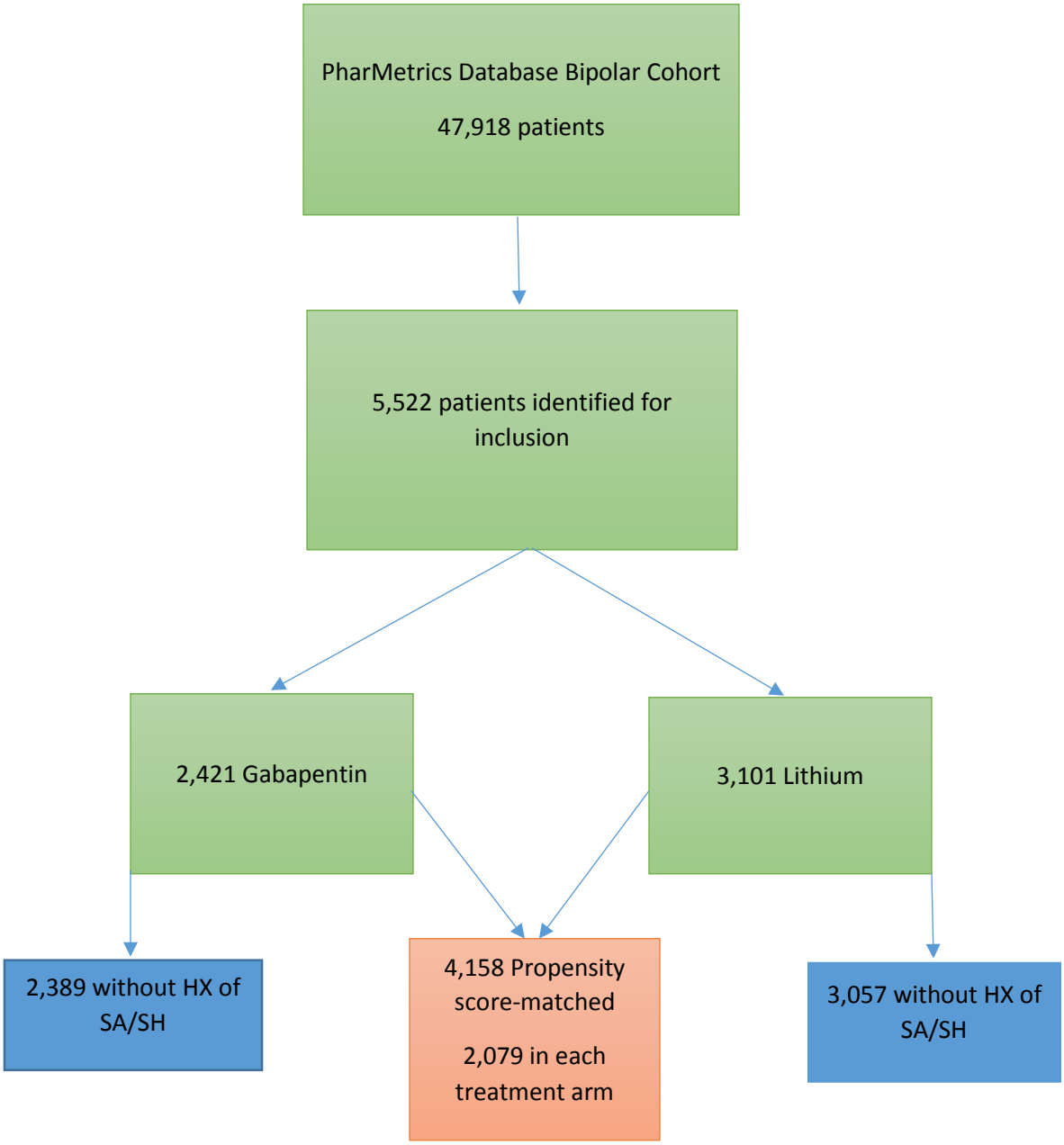

Table 1. Suicide Attempt/Self-Harm Definitions

ICD-9 Code	Definition
E950	Self-inflicted poisoning by solid or liquid substance
E951	Self-inflicted poisoning by gases in domestic use
E952	Self-inflicted poisoning by other gases and vapors
E953	Self-inflicted injury by hanging, strangulation, and suffocation
E954	Self-inflicted injury by submersion
E955	Self-inflicted injury by firearms, air guns, and explosives
E956	Self-inflicted injury by cutting and piercing instrument
E957	Self-inflicted injury by jumping from high place
E958	Self-inflicted injury by other and unspecified means
E959	Late effects of self-inflicted injury

Table 2. Anti-epileptic Medications

Carbamazepine
Divalproex
Felbamate
Lamotrigine
Levetiracetam
Oxcarbazepine
Pregabalin
Tiagabine
Topiramate
Valproate
Zonisamide

Table 3. ICD-9 Codes for Comorbidities

Cancer	140.xx-239.xx
Epilepsy	345.xx
HIV	042.xx
Pain Disorders	053, 250.6, 282.42, 282.62, 282.64, 282.69, 307.8, 307.80, 338.0, 338.1, 338.11, 338.12, 338.18, 338.19, 338.2, 338.21, 338.22, 338.28, 338.29, 338.3, 338.4, 350, 351, 352.1, 353, 353.6, 354-357, 357.2, 379.91, 388.71, 388.72, 440.22, 454.8, 524.60, 529.6, 557.9, 569.42, 577.1, 607.3, 611.71, 625.2, 625.3, 714.0, 715, 719.0, 719.4, 721.0, 721.2, 721.3, 721.90, 723.1, 724.1, 724.2, 724.3, 724.5, 729.0, 729.1, 729.2, 729.5, 780.96, 782.0, 784.0, 784.1, 786.5, 786.50, 786.52, 786.59, 787.3, 788.1, 788.9, 789.0, 789.9, 865.1, 996.7, 997.6
Psychiatric Disorders	290.xx-316.xx
Bipolar	296.0x, 296.1x, 296.4x, 296.5x, 296.6x, 296.7x, 296.8x
Major Depressive Disorder	296.2x, 296.3x, 300.4x, 311
Schizophrenia	295.0x-295.9x

Table 4. Summary Statistics, Full Gabapentin or Lithium Cohort

	Gabapentin N=2421	Lithium N=3101	P-value*
Age, mean (standard error)	43.5 (0.2)	40.6 (0.2)	<0.0001
Female, n (%)	1629 (67.3)	1821 (58.7)	<0.0001
Epilepsy, n (%)	28 (1.2)	17 (0.6)	0.02
Schizophrenia, n (%)	83 (3.4)	155 (5)	0.005
Pain Disorder, n (%)	1673 (69.1)	1546 (50)	<0.0001
Major Depressive Disorder, n (%)	1168 (48.2)	1214 (39.2)	<0.0001
Other Psychological Disorders, n (%)	1628 (67.2)	1932 (62.3)	0.0001
HIV, n (%)	17 (0.7)	4 (0.1)	0.0007
Cancer, n (%)	319 (13.2)	378 (12.2)	0.29
Antidepressants, n (%)	1909 (78.9)	1899 (61.2)	0.0001
Antipsychotics, n (%)	675 (27.9)	1097 (35.4)	<0.0001
Anticonvulsants, n (%)	453 (18.7)	433 (14)	<0.0001
Prior SA/SH, n (%)	32 (1.3)	44 (1.4)	0.82

SA/SH = Suicide attempt/self-harm

*T-test for age; Fisher's exact test for all others

Table 5. Unadjusted Incidence, Full Gabapentin or Lithium Cohort

	Gabapentin N=2421	Lithium N=3101	P-value
SA/SH, n (%)	21 (0.9)	16 (0.5)	0.13*
Study Time, days (standard error)	138.1 (2.3)	167.3 (2.2)	< 0.0001**
Total Person-Years	915.8	1421.3	
SA/SH rate per 1,000 PY	22.9	11.3	0.03***

SA/SH = Suicide attempt/self-harm

* Fisher's exact test

** T-test

*** Wald chi-square

Table 6. Summary Statistics, Subjects without Prior SA/SH Event

	Gabapentin N=2389	Lithium N=3057	P-value*
Age, mean (standard error)	43.5 (0.2)	40.7 (0.2)	<0.0001
Female, n (%)	1604 (67.1)	1792 (58.6)	<0.0001
Epilepsy, n (%)	28 (1.2)	17 (0.6)	0.02
Schizophrenia, n (%)	82 (3.4)	153 (5)	0.005
Pain Disorder, n (%)	1647 (68.9)	1518 (49.7)	<0.0001
Major Depressive Disorder, n (%)	1142 (47.8)	1178 (38.5)	<0.0001
Other Psychological Disorders, n (%)	1596 (66.8)	1890 (61.8)	0.0002
HIV, n (%)	17 (0.7)	4 (0.1)	0.0007
Cancer, n (%)	315 (13.2)	372 (12.2)	0.27
Antidepressants, n (%)	1880 (78.7)	1865 (61.0)	<0.0001
Antipsychotics, n (%)	659 (27.6)	1081 (35.4)	<0.0001
Anticonvulsants, n (%)	447 (18.7)	426 (13.9)	<0.0001

SA/SH = Suicide attempt/self-harm

*T-test for age; Fisher's exact test for all others

Table 7. Unadjusted Incidence, Subjects without Prior SA/SH Event

	Gabapentin N=2389	Lithium N=3057	P-value
SA/SH, n (%)	18 (0.8)	15 (0.5)	0.22*
Study Time, days (standard error)	138.8 (2.4)	168.0 (2.3)	<0.0001**
Total Person-Years	908.3	1407.2	
SA/SH rate per 1,000 PY	19.8	10.7	0.08***

SA/SH = Suicide attempt/self-harm

* Fisher's exact test

** T-test

*** Wald chi-square

Table 8. Summary Statistics, Pre-existing Covariates, Propensity Score-Matched Cohort

	Gabapentin N=2079	Lithium N=2079	P-value*
Age, mean (standard error)	42.2 (0.3)	42.2 (0.3)	0.9
Female, n (%)	1360 (65.4)	1338 (64.4)	0.5
Epilepsy, n (%)	11 (0.5)	8 (0.4)	0.65
Schizophrenia, n (%)	39 (1.9)	51 (2.5)	0.24
Pain Disorder, n (%)	921 (44.3)	918 (44.2)	0.95
Major Depressive Disorder, n (%)	675 (32.5)	735 (35.4)	0.05
Other Psychological Disorders, n (%)	1043 (50.2)	1022 (49.2)	0.54
HIV, n (%)	3 (0.1)	3 (0.1)	1
Cancer, n (%)	165 (7.9)	170 (8.2)	0.82
Antidepressants, n (%)	1870 (90)	1876 (90.2)	0.8
Antipsychotics, n (%)	1040 (50)	991 (47.7)	0.14
Anticonvulsants, n (%)	576 (27.7)	560 (26.9)	0.6
Prior SA/SH, n (%)	31 (1.5)	34 (1.6)	0.8

SA/SH = Suicide attempt/self-harm

*Fisher's exact test

Table 9. Summary Statistics, Concurrent Covariates, Propensity Score-Matched Cohort

	Gabapentin N=2079	Lithium N=2079	P-value*
Epilepsy, n (%)	20 (1)	12 (0.6)	0.2
Schizophrenia, n (%)	74 (3.6)	91 (4.4)	0.2
Pain Disorder, n (%)	1350 (64.9)	1186 (57.1)	<0.0001
Major Depressive Disorder, n (%)	987 (47.5)	99 (44.2)	0.04
Other Psychological Disorders, n (%)	1425 (68.5)	1310 (63.0)	0.0002
HIV, n (%)	5 (0.2)	4 (0.2)	1
Cancer, n (%)	272 (13.1)	260 (12.5)	0.6
Antidepressants, n (%)	1619 (77.9)	1542 (74.2)	0.006
Antipsychotics, n (%)	586 (28.2)	745 (35.8)	<0.0001
Anticonvulsants, n (%)	345 (16.6)	346 (16.6)	1

SA/SH = Suicide attempt/self-harm

*T-test for age; Fisher's exact test for all others

Table 10. Unadjusted Incidence, Propensity Score-Matched Cohort

	Gabapentin N=2079	Lithium N=2079	P-value
SA/SH, n (%)	20 (1)	11 (0.5)	0.15
Study Time, days (standard error)	139.5 (2.5)	168.5 (2.7)	<0.0001
Total Person-Years	794.30	959.50	
SA/SH rate per 1,000 PY	25.20	11.50	0.04

SA/SH = Suicide attempt/self-harm

* Fisher's exact test

** T-test

*** Wald chi-square

References

1. Mack A. Examination of the evidence for off-label use of gabapentin. *Journal of Managed Care Pharmacy.* 2003; 9(6):559-568.

2. Chace MJ, Zhang F, Fullerton CA, Huskamp HA, Gilden D, Soumerai SB. Intended and unintended consequences of the gabapentin off-label marketing lawsuit among patients with BPD. *Journal of Clinical Psychiatry.* 2012; 73(11):1388-1394.

3. Food and Drug Administration. Statistical review and evaluation: Antiepileptic drugs and suicidality. *U.S. Department of Health and Human Services*. 2008.

4. Food and Drug Administration. Suicidal behavior and ideation and antiepileptic drugs. 2009. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm100190.htm

5. Hesdorffer DC, Kanner AM. The FDA alert on suicidality and antiepileptic drugs: Fire or false alarm? *Epilepsia*. 2009; 50(5):978-86.

6. Ferrer P, Ballarin E, Sabate M, Vidal X, Rottenkolber M, Amelio J, Hasford J, Schmiedl S, Ibanez L. Antiepileptic drugs and suicide: A systematic review of adverse effects. *Neuroepidemiology*. 2014; 42:107-120.

7. Gibbons RD, Hur K, Brown CH, Mann JJ. Gabapentin and suicide attempts. *Pharmacoepidemiology and Drug Safety*. 2010; 19(12):1241-7.

8. Patorno E, Bohn RL, Wahl PM, Avorn J, Patrick AR, Liu J, Schneeweiss S. Anticonvulsant medications and the risk of suicide, attempted suicide, or violent death. *JAMA.* 2010; 303(14):1401-1409.

9. Collins JC, McFarland BH. Divalproex, lithium and suicide among Medicaid patients with BPD. *Journal of Affective Disorders*. 2008; 107(1-3):23-28.

10. Pugh MJV, Copeland LA, Zeber JE, Wang CH, Amuan ME, Mortensen EM, Tabares JV, Van Cott AC, Cooper TL, Cramer JA. Antiepileptic drug monotherapy exposure and suicide-related behavior in older veterans. *Journal of the American Geriatrics Society*. 2012; 60(11):2042-2047.

11. Gibbons RD, Hur K, Brown CH, Mann JJ. Relationship between antiepileptic drugs and suicide attempts in patients with BPD. *Archives of General Psychiatry*. 2009; 66(12):1354-1360.

12. Patorno, E. Letters: Antiepileptic Medications and the Risk of Suicide. *JAMA.* 2010; 304(5):522-523.

13. Suissa S. Immortal Time Bias in Pharmaco-epidemiology. *American Journal of Epidemiology*. 2008; 167(4):492-499.

14. Parsons LS. Reducing Bias in a Propensity Score Matched-Pair Sample Using Greedy Matching Techniques. *Proceedings of the Twenty-Sixth Annual SAS Users Group International Conference, Cary, NC: SAS Institute Inc.,* 2001; http://www2.sas.com/proceedings/sugi26/p214-26.pdf.

15. Fountoulakis KN, Gonda X, Siamouli M, Rihmer Z. Psychotherapeutic intervention and suicide risk reduction in bipolar disorder: A review of the evidence. *Journal of Affective Disorders*. 2009; 113:21-29.

16. Mula M, Kanner AM, Schmitz B, Schachter S. Antiepileptic drugs and suicidality: An expert consensus statement from the Task Force on Therapeutic Strategies of the ILAE Commission on Neuropsychobiology. 2013; 54(1):199-203.

Chapter 3: Conclusions and Implications for Protection of Public Health

Summary

In 2008, the FDA issued a warning that AEDs as a class cause a significant increase in the risk of suicide and suicide-related behaviors, regardless of mechanism, indication, or patient demographics [1]. They arrived at this conclusion via meta-analysis of all available placebo-controlled, randomized clinical trials of 11 anti-epileptic medications. Despite this ruling, a review of the literature shows that the issue is far from settled.

Multiple large-scale studies conducted using medical claims data have supported the FDA's decision. In a propensity score matched subgroup analysis of patients diagnosed with mood disorders, Patorno et al., 2010, found a relative risk of attempted or completed suicide of 2.0 (95% CI [1.43, 2.79]) when comparing gabapentin to topiramate [2]. Relative to lithium treatment, Collins and McFarland found an adjusted hazard rate of 1.6 for suicide attempt (not significant), and 2.6 for completed suicide ($p<0.0001$) in an Oregon Medicaid population [3]. Pugh et al., 2012, also found a significantly increased risk for suicide-related events in a cohort of older, bipolar veterans (HR = 2.56, 95% CI [1.96-4.16]) [4].

However, several similarly designed studies have arrived at the opposite conclusion. The most notable of these studies were conducted by Gibbons, Hur, Brown, Mann, 2009, who found that there was no significant increase in suicidality among bipolar patients when comparing pre-treatment rates to post-treatment rates among patients who initiate a gabapentin prescription [5]. Further, their results even suggest that gabapentin is protective, with a reported event rate ratio of 0.15 (95% CI [0.05, 0.47]). However, the Gibbons studies received heavy criticism for data and analysis flaws, as well as a significant conflict of interest in that the data and analyses were paid for by Pfizer in conjunction with pending litigation for which Gibbons would provide expert witness testimony [6,7].

In this study we re-examined the Gibbons cohort of patients diagnosed with bipolar disorder. For our analysis we selected patients who initiated a new prescription of either gabapentin or lithium in order to evaluate the association between gabapentin and suicidality. We showed a significant association between the use of gabapentin and the risk of suicidality and self-harm in patients diagnosed with bipolar disorder. Specifically, we have shown that, even after adjusting for demographics, comorbid diagnoses, concomitant medications, and a history of SA/SH, bipolar patients treated with gabapentin have approximately twice the risk of SA/SH as compared to patients treated with lithium (HR=2.3; 95% CI [1.2, 4.5]). Further, sensitivity analyses, including propensity score matching, support this conclusion.

Limitations

Our analysis is limited by fundamental, irreconcilable problems with the data set. First, because the data set was constructed specifically for the Gibbons study, we were limited by their inclusion criteria, which included the restriction to patients with two uninterrupted years of health insurance coverage. There is no way to account for the outcomes of those patients who lost coverage. More importantly, we cannot speak to rates of completed suicide, as any completed suicide would have been excluded by the “continuous insurance coverage” definition. The Gibbons study also dictated which concomitant medications were to be included. We had limited access to concomitant medication use and could not account for anything other than antidepressants, anticonvulsants, and antipsychotics. Second, because this was an observational study of insurance claims data, we have no way of measuring the severity of illness. Third, we have no way of accounting for any nonmedical treatments, such as psychotherapy. Fourth, patients were not randomized to the treatment groups, and therefore differences in SA/SH rates may be due to other, unmeasured differences between those who were prescribed gabapentin versus those who were prescribed lithium. Fifth, we cannot be certain of patient adherence to the medication. Finally, because the data were drawn from

insurance claims, there may be non-differential reporting of comorbid illnesses. For instance, it is plausible that a subject may have had a cancer diagnosis prior to the study period, but it was not noted again until after their index prescription. Thus the patient would be noted to have a concurrent cancer diagnosis, but not a pre-existing diagnosis. However, there is no reason to believe that this would disproportionately affect one arm over the other.

Strengths

Despite these limitations, we feel this study presents an accurate, rigorous examination of the data available. In so far as statistical methods allow, we attempted to mediate the potential impact of the above-mentioned shortcomings of the data. There are many strengths to our study. Chief among these is that we examined patients who initiated a new, monotherapy prescription for gabapentin or lithium. Thus we were able to isolate the potential effects of each medication. This is of particular concern, given the fact that the FDA has determined that AEDs as a class increase suicidality. Our conclusions regarding gabapentin are therefore insulated from the potential effects of other AEDs. Second, our use of Cox proportional hazards models accurately accounts for actual exposure time, in that an SA/SH event must have occurred while on the medication, and that the amount of time at risk is incorporated in the model. Though we cannot guarantee medication adherence, our definition of continuous use minimizes the amount of potentially misclassified study time. Third, our models accounted for many comorbid conditions and concomitant medications, as well as a history of suicidality. Finally, and perhaps most importantly, we measured events from the index prescription date, rather than comparing SA/SH events prior to medication to those following medication, which likely produces misleading results due to the increase in suicidal behaviors in the months preceding initial medication (and in the case of the Gibbons study, results in a protective effect for gabapentin).

With respect to the loss of data due to the Gibbons inclusion restrictions, we note that this likely resulted in an underestimation of the true effect of gabapentin. Given that a history of suicidality

is the strongest predictor of future completed suicide, we expect that the increase in SA/SH observed here would translate into a greater rate of completed suicide among patients taking gabapentin. We would have preferred to control for more concomitant medications (i.e. pain medications and benzodiazepines), but it is likely that these are correlated with the comorbid conditions for which we accounted. Though severity of illness is unmeasured, we attempted to mitigate any potential bias by using a comparably medicated control group, rather than comparing those treated with gabapentin to those who are not medically treated at all. As for nonmedical treatments, there is no reason to believe that such treatments would be differentially distributed.

Our sensitivity analyses further evaluated the effect of potential confounders, and our results remained consistent. Our first sensitivity analysis restricted the cohort to those patients without a history of SA/SH. The best predictor of future SA/SH or suicide is a history of suicidality [8]. In the current study, patients in both arms were equally likely to have had a pre-prescription SA/SH event (1.3% in the gabapentin arm and 1.4% in the lithium arm; p=0.82). However, it is possible that patients with a history significant for SA/SH in the general population may experience differential treatment assignment. In our cohort, 76 of the patients had a history of SA/SH, and of those, 4 (5.3%) experienced an SA/SH after initiating treatment. Compare this to the remainder of the cohort (n=5446), in which 33 (0.6%) subjects experienced an SA/SH event. Removing the patients with an SA/SH history did not substantially reduce the adjusted hazard ratio (1.87 95% CI [0.9, 3.8]). However, the result was no longer statistically significant; this is likely due to the reduction in power resulting from the removal of 10.8% of the events of interest.

Observational studies pose a distinct disadvantage in comparison to randomized controlled trials (RCTs) in that a subject's pre-treatment characteristics may influence both which treatment a subject receives, as well as the likelihood of a subject experiencing an event of interest. Traditional methods of dealing with these discrepancies include adjusting models for

potential confounders. In a propensity score-matched analysis, potential confounding variables are used to estimate the probability of being in the treatment group. Treatment and control subjects are then matched to each other based on their propensity for being assigned the treatment. This process creates a pseudo-experiment which mimics the result of the randomization process in a RCT, and yields treatment and control groups which are not significantly different with respect to potential pre-existing confounders. Further, because there are likely correlations between known and unknown confounding conditions and medications, our use of the propensity score-matched analysis has the added benefit of balancing the groups with respect to unknown confounders. After matching, subjects treated with gabapentin to those treated with lithium, our result remained unchanged, with a statistically significant hazard ratio of 2.1.

Discussion

Gabapentin Marketing and Legal Action

It is well-known that once a medication has been approved by the FDA for an indication, physicians can then prescribe it for any off-label condition, approved or not [9, 10]. It is illegal for a manufacturer to market a medication for anything other than its FDA-approved indication, however, the FDA does allow the use of peer-reviewed articles to disseminate information regarding the efficacy of a treatment in an off-label condition, with the stipulation that the information not be false or misleading, and that, if relied upon, the information not pose a significant risk to public health [11]. Pharmaceutical companies have used this legal loophole to market off-label uses by engaging in publication bias – intentionally withholding studies that show negative results, or reframing negative results so as to make them appear inconsequential, thereby creating the impression of proven efficacy for the off-label indications [12].

Gabapentin was approved for the treatment of epilepsy in 1993, and for post-herpetic neuralgia in 2002. Following the 2004 whistleblower litigation and the 2008 false claims litigation brought against Pfizer and Parke-Davis, Vedula, Goldman, Rona, Greene, & Dickersin, 2012, published a report detailing the internal company documents, memos, and email communications related to their gabapentin marketing strategies [10]. Documents from the 2004 litigation are available and searchable online [13]. After the initial approval, Pfizer and its marketing unit, Parke-Davis, performed several marketing assessments, evaluating the market potential for possible off-label uses, as well as evaluation of the costs associated with pursuing FDA approval versus utilizing a publication marketing strategy. Pfizer subsequently identified four potential off-label indications for gabapentin: migraine, bipolar disorder, neuropathic, and nociceptive pain [10].

Internal documents showed that Pfizer eventually decided to adopt a publication marketing strategy for bipolar disorder and neuropathic pain, with the explicit determination to withhold any negative findings, and to control the message delivered by spinning the results, and selectively choosing journals and publication timing to control the audience [10]. They achieved this primarily by sending positive results to high-impact journals in a very timely fashion, while delaying the publication of negative results, and selecting low-impact journals to minimize exposure. Vedula, Bero, Scherer, & Dickersin, 2009, identified a total of 21 studies pertaining to gabapentin, one of which was excluded from the report as it was not associated with any internal documents or communication [14]. Of the remaining 20, only 12 were published. Of these 12, 8 reported primary outcomes that differed from those stated in the protocol, including 6 trials with completely new primary outcomes not mentioned at all in the protocol. This resulted in 5 of the 8 (62.5%) trials reporting statistically significant results favoring gabapentin, suggesting an ad hoc adjustment to the analysis in order to publish positive results [14].

Pfizer's marketing strategy was highly effective. Fullerton, Busch, & Frank, 2010, studied a cohort of Florida Medicaid bipolar patients and found that prescription rates very closely

matched the national spending on marketing to psychiatrists [15]. At the height of gabapentin's popularity in 2000, Pfizer was spending approximately $2.6 million marketing to psychiatrists, and gabapentin prescriptions were being filled at a rate of 387 per 1,000 enrollees. Estimates based on the unsealed documents from a 1999 false claims lawsuit against Parke-Davis show that 83-95% of gabapentin prescriptions were for off-label indications. In 2004, Pfizer settled the lawsuit for $430 million. Reports on sales of gabapentin, however, did not show any significant decrease following the false claims settlement, indicating the efficacy with which Pfizer was able to promote the use of gabapentin for off-label, unproved indications [16].

Nivoli et al., 2012, published a review of new guidelines for the treatment of bipolar disorder [17]. The review included the World Federation of Societies of Biological Psychiatry (WPSBP), the Canadian Network for Mood and Anxiety Treatments and International Society for Bipolar Disorders (CANMAT ISBD), the British Association for Psychopharmacology (BAP), the National Institute of Clinical Excellence (NICE), and the National Health and Medical Research Council (NHMRC). Four of the five groups explicitly do not recommend gabapentin for the treatment of bipolar disorder. The fifth, BAP, simply does not mention it as an option for either first or second line treatment.

Public Health Implications

The legal and public health implications involved in this matter are complex and have profound consequences. On one hand, it is vital that patients with bipolar disorder are treated as effectively as possible. Therefore, we may question why gabapentin continues to be utilized as a treatment for bipolar disorder at all, considering it has never been proved effective in the control of manic or depressive episodes, and has been specifically noted as not effective and not recommended by leading experts in the treatment of BPD. On the other, patients with bipolar disorder have significantly higher risk of suicidality and completed suicide. Approximately 25-50% of patients with bipolar disorder will attempt suicide in their lifetime. The annual rate of

completed suicide in the bipolar population is 1%; more than 66 times greater than the rate in the general population (estimate 0.015%) [18]. It is imperative that we not exacerbate the situation via use of medications that can induce suicidality.

Fundamentally, it has been established via litigation that Pfizer acted in bad faith when it chose to aggressively market gabapentin for use in the treatment of bipolar disorder. It has been determined that they utilized deceptive and misleading tactics in order to boost and maintain sales in the face of declining market shares for its FDA-approved indications of epilepsy and post-herpetic neuralgia. Additionally, they knowingly withheld negative results from the peer-reviewed literature, and manipulated results in order to bias the literature with positive studies regarding gabapentin's efficacy. In the light of this knowledge, we have an obligation to revisit the Gibbons study, which continues to perpetuate the belief that gabapentin is protective in the bipolar population.

Pfizer has already been the subject of many tort lawsuits related to their misrepresentation of the effects of gabapentin, and the increasing body of literature suggests the medication is actually harmful in certain populations. Our analysis adds to that body of literature in support of the hypothesis that gabapentin does in fact increase suicidality in bipolar patients. We have used the Pfizer-funded data set provided to Gibbons et al., 2009, employed more appropriate methodology, and contrary to Gibbons' claims of a protective effect, have come to conclusions that are very much in agreement with the existing literature, which suggest a doubling of the risk of SA/SH.

Along with the existing body of literature, we hope that this study will steer clinicians away from prescribing gabapentin to bipolar patients. Additionally, we suggest that clinicians adopt thorough mental health screening practices when considering prescribing gabapentin to patients with diagnoses of epilepsy or pain, two conditions that are strongly associated with depression and mood disturbances. We feel the evidence strongly supports that gabapentin increases the

risk of suicidality. However, for the FDA approved indications, the risks associated with not receiving treatment may outweigh the risks associated with gabapentin [19]. Therefore, it is of the upmost importance to monitor any patient taking gabapentin.

References

1. Food and Drug Administration. Statistical review and evaluation: Antiepileptic drugs and suicidality. *U.S. Department of Health and Human Services*. 2008.
2. Patorno E, Bohn RL, Wahl PM, Avorn J, Patrick AR, Liu J, Schneeweiss S. Anticonvulsant medications and the risk of suicide, attempted suicide, or violent death. *JAMA.* 2010; 303(14):1401-1409.
3. Collins JC, McFarland BH. Divalproex, lithium and suicide among Medicaid patients with bipolar disorder. *Journal of Affective Disorders*. 2008; 107(1-3):23-28.
4. Pugh MJV, Copeland LA, Zeber JE, Wang CH, Amuan ME, Mortensen EM, Tabares JV, Van Cott AC, Cooper TL, Cramer JA. Antiepileptic drug monotherapy exposure and suicide-related behavior in older veterans. *Journal of the American Geriatrics Society*. 2012; 60(11):2042-2047.
5. Gibbons RD, Hur K, Brown CH, Mann JJ. Relationship between antiepileptic drugs and suicide attempts in patients with bipolar disorder. *Archives of General Psychiatry*. 2009; 66(12):1354-1360.
6. Patorno, E. Letters: Antiepileptic Medications and the Risk of Suicide. *JAMA.* 2010; 304(5):522-523.
7. Ferrer P, Ballain E, Sabate M, Vidal X, Rottenkolber M, Amelio J, Hasford J, Schmiedl S, Ibanez L. *Neuroepidemiology*. 2014; 42:107-120.
8. Gonda X, Pompili M, Serafini G, Montebovi F, Campi S, Dome P, Duleba T, Girardi P, Rihmer Z. Suicidal behavior in bipolar disorder: Epidemiology, characteristics, and major risk factors. *Journal of Affective Disorders*. 2012; 143:16-26.
9. Dresser R, Frader J. Off-label prescribing: a call for heightened professional and government oversight. *Journal of Law, Medicine & Ethics*. 2009; 37(3):476-486.
10. Vedula SS, Goldman PS, Rona IJ, Greene TM, Dickersin K. Implementation of a publication strategy in the context of reporting biases. A case study based on new documents from Neurontin litigation. *Trials*. 2012; 13:136.
11. Food and Drug Administration. Good reprint practices for the distribution of medical journal articles and medical or scientific reference publications on unapproved new uses of approved drugs and approved or cleared medical devices. *U.S. Department of Health and Human Services*. 2009.
12. Ghaemi SN, Shirzadi AA, Filkowski M. Publication bias and the pharmaceutical industry: The case of lamotrigine in bipolar disorder. *The Medscape Journal of Medicine*. 2008; 10(9):211.

13. Drug Industry Documents Archive. https://industrydocuments.library.ucsf.edu/drug/
14. Vedula SS, Bero L, Scherer RW, Dickersin K. Outcome reporting in industry-sponsored trials of gabapentin for off-label use. *New England Journal of Medicine*. 2009; 361(20):1963-1971.
15. Fullerton CA, Busch AB, Frank RG. The rise and fall of gabapentin for bipolar disorder: a case study on off-label pharmaceutical diffusion. *Medical Care*. 2010; 48(4):372-379.
16. Kesselheim AS, Darby D, Studdert DM, Glynn R, Levin R, Avorn J. False claims act prosecution did not deter off-label drug use in the case of Neurontin. *Health Affairs*. 2011; 30(12):2318-2327.
17. Nivoli AMA, Murru A, Goikolea JM, Crespo JM, Montes JM, Gonzalez-Pinto A, Garcia-Portilla P, Bobes J, Saiz-Ruiz J, Vieta E. New treatment guidelines for acute bipolar mania: A critical review. *Journal of Affective Disorders*. 2012; 140:125-141.
18. Fountoulakis KN, Gonda X, Siamouli M, Rihmer Z. Psychotherapeutic intervention and suicide risk reduction in bipolar disorder: A review of the evidence. *Journal of Affective Disorders*. 2009; 113:21-29.
19. Mula M, Kanner AM, Schmitz B, Schachter S. Antiepileptic drugs and suicidality: An expert consensus statement from the Task Force on Therapeutic Strategies of the ILAE Commission on Neuropsychobiology. 2013; 54(1):199-203.