Background: Gabapentin is prescribed for seizures and pain and has efficacy for treating alcohol use disorder (AUD) starting at doses of 900 milligrams per day (mg/d). Recent evidence suggests safety concerns associated with gabapentin including adverse neurologic effects. Individuals with hepatitis C (HCV), HIV, or AUD may be at increased risk due to comorbidities and potential medication interactions.

Methods: We identified patients prescribed gabapentin for ≥ 60 days for any indication between 2002 and 2015. We propensity-score matched each gabapentin-exposed patient with up to 5 gabapentin-unexposed patients. We followed patients for 2 years or until diagnosed with (i) falls or fractures, or (ii) altered mental status using validated ICD-9 diagnostic codes. We used Poisson regression to estimate incidence rates and relative risk (RR) of these adverse events in association with gabapentin exposure overall and stratified by age, race/ethnicity, sex, HCV, HIV, AUD, and dose.

Results: Incidence of falls or fractures was 1.81 per 100 person-years (PY) among 140,310 gabapentin-exposed and 1.34/100 PY among 431,408 gabapentin-unexposed patients (RR 1.35, 95% confidence interval [CI] 1.28 to 1.44). Incidence of altered mental status was 1.08/100 PY among exposed and 0.97/100 PY among unexposed patients, RR of 1.12 (95% CI 1.04 to 1.20). Excess risk of falls or fractures associated with gabapentin exposure was observed in all subgroups except patients with HCV, HIV, or AUD; however, these groups had elevated incidence regardless of exposure. There was a clear dose–response relationship for falls or fractures with highest risk observed among those prescribed ≥ 2,400 mg/d (RR 1.90, 95% CI 1.50 to 2.40). Patients were at increased risk for altered mental status at doses 600 to 2,399 mg/d; however, low number of events in the highest dose category limited power to detect a statistically significant association ≥ 2,400 mg/d.

Conclusions: Gabapentin is associated with falls or fractures and altered mental status. Clinicians should be monitoring gabapentin safety, especially at doses ≥ 600 mg/d, in patients with and without AUD.

Key Words: Gabapentin, Neurologic Effects, Electronic Health Records, Alcohol Use Disorder, Chronic Hepatitis C, HIV Infection.
medication in the United States (IQVIA Institute, 2018). Prescribing rates of gabapentin have increased considerably in recent years partially due to promotion of gabapentin for on- and off-label uses (Steinman et al., 2006) as well as the perception that it represents a safe alternative to opioids for treating chronic pain (Goodman and Brett, 2017).

However, gabapentin presents important safety concerns including neurologic adverse effects, such as ataxia, dizziness, and somnolence (Meng et al., 2014; Shanthanna et al., 2017; Wiffen et al., 2017). This is of particular concern for populations who may be at increased risk for adverse effects, such as individuals with hepatitis C (HCV), HIV, and AUD. These patients may be at greater risk of neurologic adverse events due to medical and psychiatric comorbidities and potential medication interactions. As alterations in mental status and coordination can lead to falls, fractures are a particular concern due to the association of HIV infection with fragility fractures (Womack et al., 2011) and AUD with osteoporosis and osteopenia (Berg et al., 2008).

Given the widespread prescribing of gabapentin and its potential utility in decreasing alcohol consumption among treatment-seeking and non-treatment-seeking populations (Rentsch et al., 2019), we sought to determine its association with events often linked with neurologic effects of dizziness, ataxia, and somnolence among patients receiving gabapentin for any indication, specifically falls or fractures (Ishida et al., 2018) and altered mental status. We further assessed whether these effects differed in demographic and clinical subpopulations at higher risk for these events, including patients with and without HCV, HIV, and AUD.

MATERIALS AND METHODS

Study Population

We used electronic health record (EHR) data available through the US Department of Veterans Affairs (VA) national Corporate Data Warehouse (CDW). The VA is the largest integrated healthcare system in the United States and comprises over 800 community outpatient clinics, 150 hospitals and medical centers, and 120 nursing homes. We extracted data on all patients born between 1945 and 1965 who had at least 1 outpatient visit on or after 1 October 1999, which included approximately half of all Veterans in care. This study has been approved by the institutional review boards of the VA Connecticut Healthcare System and Yale School of Medicine, granted a waiver of informed consent, and deemed Health Insurance Portability and Accountability Act compliant.

We included patients who did (gabapentin exposed) and did not (gabapentin unexposed) receive gabapentin dispensed at VA pharmacies. We did not consider other gabapentinoids (e.g., pregabalin or gabapentin enacarbil) in this analysis as they are not commonly prescribed in the VA. The gabapentin-exposed group included all patients who received 2 or more gabapentin fills for at least 60 continuous days, for any indication, between January 1, 2002, and March 30, 2015, from the following VA clinics: primary care, mental health, neurology, general internal medicine, physical medicine and rehabilitation services, pain, podiatry, orthopedics, women’s clinic, psychiatry, substance use, and rheumatology. These clinics were chosen because they were the source of most gabapentin prescriptions. To ensure that unexposed patients came from the same source population and had an equal opportunity to receive gabapentin, we randomly selected one outpatient visit date per calendar year to identify patients who attended one of the listed clinics but never received gabapentin.

To allow us to follow exposed and unexposed patients over similar calendar time, we created an “index date” (also referred to as “baseline”), which was defined as the first fill date for gabapentin-exposed patients and the random outpatient visit date for unexposed patients. We identified the first prescription for gabapentin during the study period and required a 180-day washout period so as to identify new episodes of gabapentin exposure. We excluded patients with no outpatient care in the year prior to their index date, because of unknown recent medical history.

Propensity Score Model and Matching

In clinical trials, randomization is used to balance the distribution of all potential confounders across treatment groups. To emulate randomization using observational data, we used propensity score matching. This was done by first modeling the probability (i.e., propensity) of receiving the treatment of interest as a function of all measured covariates (Brookhart et al., 2006). Exposed patients were then matched to unexposed patients with a similar propensity. Matching by propensity score creates balanced exposure groups similar to treatment allocation in a randomized controlled trial (Austin, 2011), thus addressing concerns of confounding by indication. Unexposed patients with very low propensity and exposed patients with very high propensity are unlikely to match, which is akin to inclusion and exclusion criteria of a trial.

In our study, propensity scores were used to account for the probability of being prescribed gabapentin given a set of covariates that are associated with both gabapentin receipt and neurologic adverse events or associated only with neurologic adverse events. Propensity scores (i.e., the predicted probability of gabapentin exposure) were estimated using a multivariable logistic regression model. Variables used in the propensity score models were selected a priori based on clinical knowledge (Hernan et al., 2002) and included the following: year of index date, age at baseline, race/ethnicity, smoking status, body mass index at baseline, site prescribing pattern (the proportion of patients who initiated gabapentin stratified by year), laboratory values closest to the index date (including hemoglobin, international normalized ratio, triglycerides), HCV status, HIV status, history of seizure prior to baseline, diabetes complications severity index (Young et al., 2008) at baseline, history of pain diagnoses prior to baseline (including neuropathy, osteoarthritis, or pain in the abdomen, back, chest, extremity, or neck, headache, or fracture), and history of medical and psychiatric conditions prior to baseline (including atrial fibrillation, myocardial infarction/coronary artery disease, peripheral vascular disease, diabetes, nephrolithiasis, glomerulonephritis, hyperlipidemia, pancreatitis, drug use disorders, posttraumatic stress disorder (PTSD), major or other depression, anxiety, bipolar disorder, schizophrenia, and schizoaffective disorder). We also included variables that captured attendance to clinics (including primary care, dialysis, diabetic retinal screening, rheumatology, infectious disease, nephrology, neurology, pain, allergy, chiropractic, dental, diabetes, emergency department, electrocardiogram laboratory, ophthalmology, hematology, oncology, homeless program, nutrition, orthopedics, substance use, mental health, PTSD), frequency of all-cause hospitalizations, and the total number of unique clinics visited in the year prior to baseline. Lastly, variables denoting receipt of other prescriptions at baseline to treat pain (including benzodiazepines, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, muscle relaxants, and antidepressants) and seizures were included in the model. Interaction terms were explored for significance, and 5 were kept in the final model (all p < 0.05). The model c-statistic was 0.89 indicating adequate discrimination between gabapentin-exposed and gabapentin-unexposed patients ( Hosmer and Lemeshow, 2000). Since the distribution of propensity scores for exposed patients was
different than that of unexposed patients, we used propensity score matching to exclude nonexchangeable unexposed patients (i.e., those with extremely low probability of gabapentin exposure) (Fig. 1) (Spoendlin et al., 2016). Each exposed patient was matched to up to 5 unexposed patients in the same calendar year, using a greedy matching algorithm (Cormen, 2009).

Clinical Subpopulations

For all conditions, we required 1 inpatient or 2 outpatient diagnostic codes using the International Classification of Diseases, 9th revision (ICD-9). HCV infection was defined by any confirmatory HCV RNA test or ICD-9 diagnostic codes 070.41/0.44; 070.51/0.54; 070.70/0.71; or V02.62. HIV status was determined by ICD-9 diagnostic codes 042, 044, or V08. AUD status was determined by ICD-9 diagnostic codes 303.X or 305 to 305.03 at any time prior to baseline. The date of AUD diagnosis was used to categorize AUD status into 3 mutually exclusive categories: never, lifetime (before the year prior to the index date), or current (1 year prior to or 180 days after the index date). Patients with both lifetime and current AUD diagnoses were classified as current.

Fig. 1. Distribution of propensity scores of gabapentin exposure before and after propensity score matching. Panel (A): Before matching. Panel (B): After matching

(A) Before matching

Median (interquartile range)
Exposed: 0.09 (0.03-0.21)
Unexposed: 0.01 (0.004-0.02)

(B) After matching

Median (interquartile range)
Exposed: 0.07 (0.03-0.13)
Unexposed: 0.04 (0.02-0.07)
Neurologic Adverse Events and Follow-Up

We used ICD-9 codes to define falls or fractures (805.2X-805.7, 812.XX, 820.XX, E882-E885, E888) and altered mental status (291, 291.1, 292.81, 293, 293.1, 298.2, 780.09, 780.97). These ICD-9 codes were selected to be consistent with previous literature (Hope et al., 2014; Pugh et al., 2015; Thyagarajan et al., 2013; Womack et al., 2011). We excluded patients diagnosed with any of these events in the year preceding their index date.

Patients were followed a maximum of 2 years from their index date to the first occurrence of any outcome, last VA visit, death, or September 30, 2015. Additionally, gabapentin-exposed patients were censored 30 days after the end of their last gabapentin prescription (allowing for a maximum 30-day gap between fills). To ensure equal follow-up time within matched sets, unexposed patients were censored at the total follow-up time of their matched exposed patient.

Statistical Analyses

We used standardized differences (Austin, 2009) to examine balance between exposed and unexposed patients included in the full and propensity-score matched sample. We estimated incidence rates (IR) for exposed and unexposed patients for each outcome. We then used multivariable Poisson regression models to estimate exposure rate ratios (RR) and 95% confidence intervals (CI) for the relative risk of a neurologic adverse event in association with exposure to gabapentin. We performed subgroup analyses by age (<60 or ≥60 years), race/ethnicity (white, black, or Hispanic), sex (male or female), HCV status, HIV status, and AUD (never, lifetime, or current). Finally, we investigated association of initial gabapentin dose with neurologic adverse events (<600 mg, 600 to 899 mg, 900 to 1,199 mg, 1,200 to 1,799 mg, 1,800 to 2,399 mg, and ≥2,400 mg). All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Sample

We identified 431,920 gabapentin-exposed patients and 2,576,410 gabapentin-unexposed patients eligible for propensity score matching. The matching process resulted in 54,878 (39.1%) gabapentin-exposed patients with 5 unexposed matches, 8,475 (6.0%) with 412,577 (9.0%) with 321,007 (15.0%) with 2, and 43,373 (30.9%) with 1 matched unexposed patient. Thus, the analytic sample consisted of 140,310 exposed and 431,408 unexposed patients.

Before propensity score matching, the distribution of baseline characteristics significantly differed between gabapentin-exposed and gabapentin-unexposed patients (Table 1). Compared to gabapentin-exposed patients who matched to unexposed patients, gabapentin-exposed patients who did not match had similar proportions with HCV, HIV, or current AUD, were more likely to have comorbidities, particularly neuropathic pain (28%) and be prescribed other medications particularly opioids (30%) and muscle relaxants (18%) (Table S1). The median (interquartile range) propensity score in exposed patients who did not match was 0.11 (0.03 to 0.27), higher than those who were matched 0.07 (0.03 to 0.13). In the matched sample, gabapentin-exposed and gabapentin-unexposed patients were well balanced. Median follow-up time was 137 days (IQR 100 to 269 days). Among exposed patients in the analytic sample, 38%, 20%, 28%, 7%, 5%, and 3% were initially prescribed daily doses of gabapentin <600 mg, 600 to 899 mg, 900 to 1,199 mg, 1,200 to 1,799 mg, 1,800 to 2,399 mg, and ≥2,400 mg, respectively.

Rates of Adverse Events

Overall in the matched sample, the incidence rate for falls or fractures was 1.81 per 100 person-years (PY) among exposed and 1.34/100 PY among unexposed patients, and for altered mental status 1.08/100 PY among exposed and 0.97/100 PY among unexposed patients (Table 2). Compared to unexposed patients, those exposed to gabapentin were 35% more likely (95% confidence interval [CI] 1.28 to 1.44) to experience a fall or fracture and 12% more likely (95% CI 1.04 to 1.20) to experience altered mental status (Fig. 2).

Subgroup Analyses

Compared to the overall sample, incidence rates for both neurologic adverse events were greater among those with HCV infection, HIV infection, or current AUD diagnosis. Although absolute incidence was higher, the relative risk associated with gabapentin exposure was attenuated (Table 2). The rate of falls or fractures for patients with HCV infection was 2.71/100 PY among exposed and 2.42/100 PY among unexposed (rate ratio [RR] 1.12, 95% CI 0.94 to 1.32). For patients with HIV infection, rates were 2.00/100 PY among exposed and 1.50/100 PY among unexposed (RR 1.34, 95% CI 0.74 to 2.43). For patients with current AUD diagnosis, rates were 2.84/100 PY among exposed and 2.62/100 PY among unexposed (RR 1.08, 95% CI 0.94 to 1.25). In all other subgroups, excess risk associated with gabapentin exposure persisted (Fig. 2). Similar results were observed for altered mental status in the various subgroups.

We further stratified exposed patients by dose of gabapentin. There was a clear dose–response relationship for falls or fractures with relative risks increasing from 1.23 (95% CI 1.13 to 1.34) for <600 mg/d to 1.90 (95% CI 1.50 to 2.40) for ≥2,400 mg/d (Table 3). Patients were at elevated risk for altered mental status at doses ≥600 mg/d; however, associations in dose categories ≥1,800 mg/d were not statistically significant, possibly due to few events in these higher dose categories.

DISCUSSION

In this national study of over 500,000 patients aged between 36 and 70 years, gabapentin-exposed patients had increased incidence of neurologic adverse events compared to unexposed patients and were 35% more likely to experience a fall or fracture and 12% more likely to experience altered mental status. Patients with HCV infection, HIV infection, or a current AUD diagnosis had elevated rates of...
Our overall finding that gabapentin-exposed patients were more likely to experience neurologic adverse events is consistent with several studies. A systematic review and meta-analysis evaluating the safety of gabapentinoids in chronic low back pain found that patients receiving gabapentin were significantly more likely to report dizziness, fatigue, and difficulties with mentation compared to placebo (Shanthanna et al., 2017). Similarly, a Cochrane Collaborative review of 37 randomized controlled trials examining gabapentin for chronic neuropathic pain found that adults taking gabapentin experienced significantly more gait disturbance, dizziness, and somnolence compared to those receiving placebo (Wiffen et al., 2017). A meta-analysis of 7 randomized controlled trials involving a total of 2,039 patients found that patients given gabapentin for the treatment of postherpetic neuralgia were significantly more likely to experience ataxia, dizziness, and somnolence (Meng et al., 2014). Another meta-analysis of 7 randomized controlled trials assessing safety and efficacy of different doses of gabapentin for postherpetic neuralgia found that gabapentin at 1,800 mg/d was significantly associated with dizziness and somnolence and the risk of these adverse events increased at doses of 2,400 to 3,600 mg/d (Wang and Zhu, 2017). Unlike these studies that examined adverse effects such as dizziness and ataxia, we focused on falls and fractures, which are less reported in the literature. One large observational study among 140,899 Medicare-covered adults receiving hemodialysis found that gabapentin was associated with 55% increased risk of falls and 38% increased risk of fractures (Ishida et al., 2018).

Despite evidence demonstrating gabapentin’s neurologic adverse events especially when used for pain, its use for treating individuals with AUD is generally considered safe. One randomized controlled trial evaluating the impact of gabapentin dose on alcohol-related outcomes among 150 patients with current AUD reported no significant differences in the all neurologic adverse events compared to overall rates, but did not demonstrate increased risk of neurologic events when exposed to gabapentin. Our findings also showed a positive dose–response relationship for falls or fractures at all doses with greatest risk of occurring at gabapentin doses ≥ 2,400 mg/d and increased risk of altered mental status at doses ≥ 600 mg/d.

Our overall finding that gabapentin-exposed patients were more likely to experience neurologic adverse events is consistent with several studies. A systematic review and meta-analysis evaluating the safety of gabapentinoids in chronic low back pain found that patients receiving gabapentin were significantly more likely to report dizziness, fatigue, and difficulties with mentation compared to placebo (Shanthanna et al., 2017). Similarly, a Cochrane Collaborative review of 37 randomized controlled trials examining gabapentin for chronic neuropathic pain found that adults taking gabapentin experienced significantly more gait disturbance, dizziness, and somnolence compared to those receiving placebo (Wiffen et al., 2017). A meta-analysis of 7 randomized controlled trials involving a total of 2,039 patients found that patients given gabapentin for the treatment of postherpetic neuralgia were significantly more likely to experience ataxia, dizziness, and somnolence (Meng et al., 2014). Another meta-analysis of 7 randomized controlled trials assessing safety and efficacy of different doses of gabapentin for postherpetic neuralgia found that gabapentin at 1,800 mg/d was significantly associated with dizziness and somnolence and the risk of these adverse events increased at doses of 2,400 to 3,600 mg/d (Wang and Zhu, 2017). Unlike these studies that examined adverse effects such as dizziness and ataxia, we focused on falls and fractures, which are less reported in the literature. One large observational study among 140,899 Medicare-covered adults receiving hemodialysis found that gabapentin was associated with 55% increased risk of falls and 38% increased risk of fractures (Ishida et al., 2018).

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A meta-analysis of 7 placebo-controlled randomized controlled trials evaluating efficacy of gabapentin for treating AUD also found no serious adverse events reported with gabapentin exposure (Kranzler et al., 2019). Similarly, we found less than 10% excess risk (not statistically significant) of adverse events associated with gabapentin exposure among patients with current AUD. However, a recent randomized controlled trial examining the efficacy of gabapentin on AUD treatment outcomes among 90 patients with alcohol withdrawal symptoms found significantly more reports of mild to moderate dizziness in those receiving gabapentin versus placebo (Anton et al., 2020). Additionally, a multisite clinical trial evaluating the safety and efficacy of gabapentin enacarbil extended-release (GE-XR) in 346 participants with moderate to severe AUD reported no serious adverse events related to medication use, but did find significantly greater rates of fatigue (25.9% vs. 15.5%; \( p = 0.022 \)), somnolence (17.6% vs. 9.5%; \( p = 0.038 \)), and tremor (5.9% vs. 0.6%; \( p = 0.010 \)), as well as a nonsignificant increase for dizziness (21.2% vs. 13.7%; \( p = 0.085 \)) in the GE-XR group versus placebo group (Falk et al., 2019).

Compared to overall rates, we found that patients with current AUD had greater rates of neurologic adverse events regardless of gabapentin exposure, suggesting that these patients represent a particularly vulnerable population at risk for falls, fractures, and altered mental status. Given the growing body of evidence supporting gabapentin’s safety and efficacy in treating AUD (Anton et al., 2020; Kranzler et al., 2019; Mason et al., 2014), these baseline risks among current AUD should be considered alongside the potential benefits gabapentin treatment in this population. Among trials that found significantly greater rates of adverse events among gabapentin-exposed patients, these events were reported as mild to moderate (Anton et al., 2020; Falk et al., 2019; Pani et al., 2014). Furthermore, Anton and
colleagues (2020) reported significantly more dizziness in those receiving gabapentin versus placebo, but the presence or absence of dizziness did not significantly account for gabapentin’s effectiveness. Importantly, these clinical trials included only medically stable patients who were not using substances other than alcohol and nicotine, and thus may not reflect our study sample or generalize to other treatment settings.

Similar to patients with current AUD, our subgroup analysis of patients with HCV and HIV demonstrated elevated incidence of adverse events regardless of gabapentin exposure, which may reflect baseline risk for these adverse

**Table 3.** Dose-Specific Rates of Neurologic Adverse Events Among 140,310 Gabapentin-Exposed Patients and 1:5 Propensity-Score Matched Unexposed Controls

| Dose, milligrams | # Events | Rate (95% CI) | RR (95% CI) | p-value | # Events | Rate (95% CI) | RR (95% CI) | p-value |
|------------------|---------|---------------|-------------|---------|---------|---------------|-------------|---------|
|                  | Fall or fracture | | | | Altered mental status | | |
| ≥2,400           | 71      | 2.56 (2.03 to 3.23) | 1.90 (1.50 to 2.40) | <0.0001 | 33      | 1.19 (0.84 to 1.67) | 1.21 (0.86 to 1.71) | 0.2724 |
| 1,800 to 2,399   | 92      | 1.92 (1.57 to 2.36) | 1.43 (1.16 to 1.76) | 0.0008 | 60      | 1.25 (0.97 to 1.61) | 1.28 (0.99 to 1.65) | 0.0597 |
| 1,200 to 1,799   | 124     | 2.05 (1.72 to 2.45) | 1.52 (1.27 to 1.82) | <0.0001 | 80      | 1.32 (1.06 to 1.65) | 1.35 (1.08 to 1.69) | 0.0082 |
| 900 to 1,199     | 466     | 1.98 (1.80 to 2.16) | 1.47 (1.33 to 1.62) | <0.0001 | 294     | 1.25 (1.11 to 1.40) | 1.27 (1.13 to 1.43) | <0.0001 |
| 600 to 899       | 320     | 1.76 (1.58 to 1.96) | 1.31 (1.17 to 1.47) | <0.0001 | 215     | 1.18 (1.03 to 1.35) | 1.21 (1.05 to 1.39) | 0.0082 |
| <600             | 590     | 1.66 (1.53 to 1.79) | 1.23 (1.13 to 1.34) | <0.0001 | 319     | 0.90 (0.80 to 1.00) | 0.91 (0.81 to 1.03) | 0.1260 |
| Unexposed        | 3,545   | 1.35 (1.30 to 1.39) | Ref | | 2,580   | 0.98 (0.94 to 1.02) | Ref | |

RR, rate ratio; CI, confidence interval. Rates per 100 person-years.
outcomes due to increased rates of medical and psychiatric comorbidities and potential medication interactions (Evon et al., 2018; Ruzicka et al., 2019). In contrast to our findings, one small randomized controlled trial comparing the effect of gabapentin with placebo in HIV-associated sensory neuropathy found that participants receiving gabapentin were more likely to report somnolence (12/15 for gabapentin and 2/11 for placebo; \( p = 0.006 \)), dizziness (9/15 for gabapentin and 5/11 for placebo; \( p = 0.305 \)), and gait disturbance (7/15 for gabapentin and 3/11 for placebo; \( p = 0.357 \)) (Hahn et al., 2004).

Notably, we observed a dose–response relationship for adverse events consistent with findings of a meta-analysis examining gabapentin safety among patients with postherpetic neuralgia (Wang and Zhu, 2017). This study reported increased risk of adverse outcomes starting at gabapentin doses of \( \geq 1,800 \text{ mg/d} \), whereas we demonstrated increased risk at lower doses of \( \geq 600 \text{ mg/d} \). These findings are particularly relevant when considering the use of gabapentin to treat AUD, as current evidence suggests greater impact of gabapentin on reducing alcohol consumption at higher doses of \( \geq 1,500 \text{ mg/d} \) (Mason et al., 2014; Rentsch et al., 2019). However, it is important to note that gabapentin has been shown to improve AUD outcomes even at doses as low as 900 mg/d (Mason et al., 2014), which may reduce the risk of adverse consequences. Our finding of continued gabapentin prescribing at low or subtherapeutic doses despite the apparent risk of adverse events may reflect a desire among clinicians to prescribe nonopioid medications for pain (Goodman and Brett, 2017).

This research differs from recent safety studies of gabapentin use in a number of important ways. First, we evaluated the association of gabapentin with neurologic adverse events in a real-world setting among patients who were prescribed gabapentin for any indication. Second, we addressed methodological challenges inherent to observational study designs by applying uniform exclusion criteria for exposed and unexposed patients, evaluating incident exposures, setting an index date for exposed and unexposed patients, and using propensity score matching to account for confounding by indication. Finally, our study included a large sample size of approximately 140,000 gabapentin-exposed patients, which to our knowledge is the largest study to date examining gabapentin safety in a real-world setting.

There are limitations to our work. Due to characteristics of individuals who access care in the VA healthcare system, our sample was enriched with men and patients with multiple medical comorbidities, which may not generalize to other clinical settings. Some of our analyses lacked adequate power due to small samples in certain patient subgroups, including patients with HIV infection. We were also unable to obtain proxy measures to capture adverse outcomes that were not diagnosed using ICD-9 codes, which may underestimate the rate of adverse events. Only one-third of the gabapentin-exposed patients in our cohort were propensity-score matched, although there was no significant difference of HCV, HIV, or AUD prevalence between those who did and did not match. Our findings may not generalize to those with stronger indications for gabapentin. Despite these limitations, we believe our findings provide novel information on the safety of gabapentin use and highlight the risk of falls, fractures, and altered mental status among patients from a large national integrated healthcare system.

This work has important implications for researchers and clinicians. We used real-world data to demonstrate that gabapentin is associated with increased risk of falls, fractures, and altered mental status at doses \( \geq 600 \text{ mg/d} \), which should be carefully considered by clinicians. The widespread prescribing of gabapentin for various conditions, which contrasts with the limited use of FDA-approved medications for AUD, suggests that clinicians are familiar with gabapentin and may feel more comfortable prescribing it for AUD treatment. Such comfort with prescribing gabapentin paired with growing evidence to support its efficacy in treating AUD (Anton et al., 2020; Kranzler et al., 2019; Mason et al., 2014; Pani et al., 2014) may help expand the number of individuals with AUD receiving effective medication treatment. However, these possible benefits must be weighed against potential risks. There is evidence suggesting nonmedical use of gabapentin to achieve euphoric effects, particularly in individuals with substance use disorders (Peckham et al., 2017; Smith et al., 2016). Although gabapentin misuse has been reported primarily in individuals with opioid and polysubstance use rather than in those with AUD alone, clinicians should consider monitoring for medication misuse and diversion when prescribing gabapentin. Although we did not find an excess risk of adverse events among gabapentin-exposed patients with current AUD, our findings indicate that these patients are predisposed to falls, fractures, and altered mental status that may reflect complications of acute and chronic alcohol use, such as intoxicating effects, advanced liver disease, and peripheral neuropathy. More research is needed to clarify predisposing risk factors and drug interactions that may increase these neurologic adverse events in patients with AUD to guide risk stratification and to examine gabapentin safety at higher doses associated with improved AUD outcomes.

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**CONFLICTS OF INTEREST**

The authors declare no conflict of interest.

**REFERENCES**

Anton RF, Latham P, Voronin K, Book S, Hoffman M, Prisciandaro J, Bristol E (2020) Efficacy of gabapentin for the treatment of alcohol use...
disorder in patients with alcohol withdrawal symptoms. JAMA Intern Med 180:728.

Austin PC (2009) Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med 28:3083–3107.

Austin PC (2011) An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivar Behav Res 46:399–424.

Berg KM, Kunins HV, Jackson JL, Nahvi S, Chaudhry A, Harris KA Jr, Malik R, Arstenn JH (2008) Association between alcohol consumption and both osteoporotic fracture and bone density. Am J Med 121:406–418.

Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Sturmer T (2006) Variable selection for propensity score models. Am J Epidemiol 163:1140–1150.

Cormen TH (2009) Introduction to Algorithms. MIT Press, Cambridge, MA.

Evron DM, Stewart PW, Amador J, Serper M, Lok AS, Sterling RK, Sarkar S, Golin CE, Reeve BB, Nelson DR, Reau N, Lim JK, Reddy KR, di Biasceglie AM, Fried MW (2018) A comprehensive assessment of patient reported symptom burden, medical comorbidities, and functional well being in patients initiating direct acting antiviral therapy for chronic hepatitis C: Results from a large US multi-center observational study. PLoS One 13:e0196908.

Falk DE, Ryan ML, Fertig JB, Devine EG, Cruz R, Brown ES, Burns H, Salloum IM, Newport DJ, Mendelson J, Galloway G, Kampman K, Brooks C, Green AE, Brunette MF, Rosenthal RN, Dunn KE, Strain EC, Ray L, Shoptaw S, Ait-Daoud Tsiouririne N, Gunderson EW, Ransom J, Scott C, Leggio L, Caras S, Mason BJ, Litten RJ, National Institute on Alcohol Abuse and Alcoholism Clinical Investigations Group (NCIGC) Study Group (2019) Gabapentin enacarbil extended-release for alcohol use disorder: a randomized, double-blind, placebo-controlled, multisite trial assessing efficacy and safety. Alcohol Clin Exp Res 43:158–169.

Ghinea N, Lipworth W, Kerridge I (2015) Evidence, regulation and ‘rational’ prescribing: the case of gabapentin for neuropathic pain. J Eval Clin Pract 21:28–33.

Goodman CW, Brett AS (2017) Gabapentin and pregabalin for pain - is increased prescribing a cause for concern? N Engl J Med 377:411–414.

Hahn K, Arendt G, Braun JS, von Giesen HJ, Husstedt IW, Maschke M, Hahn K, Arendt G, Braun JS, von Giesen HJ, Husstedt IW, Maschke M, von Giesen HJ, Husstedt IW, Maschke M (2014) Gabapentin and pregabalin for pain - is increased prescribing a cause for concern? N Engl J Med 377:411–414.

Hank K, Arendt G, Braun JS, von Giesen HJ, Husstedt IW, Maschke M, Hahn K, Arendt G, Braun JS, von Giesen HJ, Husstedt IW, Maschke M, von Giesen HJ, Husstedt IW, Maschke M (2014) Gabapentin and pregabalin for pain - is increased prescribing a cause for concern? N Engl J Med 377:411–414.

Hernan MA, Hernandez-Diaz S, Werler MM, Mitchell AA (2002) Causal knowledge as a prerequisite for confounding evaluation: an application to birth defects epidemiology. Am J Epidemiol 155:176–184.

Hope C, Estrada N, Weir C, Teng CC, Damal K, Sauer BC (2014) Documentation of delirium in the VA electronic health record. BMC Res Notes 7:208.

Hosmer D, Lemeshow S (2000) Applied Logistic Regression. John Wiley and Sons, New York, NY.

IQVIA Institute (2018) Medicines Use and Spending in the U.S.: A Review of 2017 and Outlook to 2022. IQVIA Institute, Parsippany, NJ.

Ishida JH, McCulloch CE, Steinman MA, Grimes BA, Johansen KL (2018) Gabapentin and pregabalin use and association with adverse outcomes among hemodialysis patients. J Am Soc Nephrol 29:1970–1978.

Kesselheim AS, Darby D, Studdert DM, Glynn R, Levin R, Avorn J (2011) False Claims Act prosecution did not deter off-label drug use in the case of neurontin. Health Aff (Millwood) 30:2318–2327.

Kranzler HR, Feinn R, Morris P, Hartwell EE (2019) A meta-analysis of the efficacy of gabapentin for treating alcohol use disorder. Addiction 114:1547–1555.

Mason BJ, Quello S, Goodell V, Shadan F, Kyle M, Begovic A (2014) Gabapentin treatment for alcohol dependence: a randomized clinical trial. JAMA Intern Med 174:70–77.

Meng FY, Zhang LC, Liu Y, Pan LH, Zhu M, Li CL, Li YW, Qian W, Liang R (2014) Efficacy and safety of gabapentin for treatment of postherpetic neuralgia: a meta-analysis of randomized controlled trials. Minerva Anestesiologica 80:556–567.

Pani PP, Trogu E, Pacini M, Maremmani I (2014) Anticonvulsants for alcohol dependence. Cochrane Database of Syst Rev 2:CD008544.

Peckham AM, Fairman KA, Sclar DA (2017) Policies to mitigate nonmedical use of prescription medications: how should emerging evidence of gabapentin misuse be addressed? Expert Opin Drug Saf 17:519–523.

Pugh MJ, Orman JA, Jaramillo CA, Salinsky MC, Eapen BC, Towne AR, Amuan ME, Roman G, McNamme SD, Kent TA, McMillan KK, Hamid H, Graffman JH (2015) The prevalence of epilepsy and association with traumatic brain injury in veterans of the Afghanistan and Iraq wars. J Head Trauma Rehabil 30:29–37.

Rentsch CT, Fiellin DA, Bryant KJ, Justice AC, Tate JP (2019) Association between gabapentin receipt for any indication and AUDIT-C scores among clinical sub-populations with and without alcohol use disorder. Alcohol Clin Exp Res 43:522–530.

Ruzicka DJ, Imai K, Takahashi K, Naito T (2019) Greater burden of chronic comorbidities and co-medications among people living with HIV versus people without HIV in Japan: a hospital claims database study. J Infect Chemother 25:89–95.

Shanthanna H, Gilron I, Rajarathinam M, Alamri R, Kamath S, Thabane L, Devereaux PJ, Bhandari M (2017) Benefits and safety of gabapentinoids in chronic low back pain: a systematic review and meta-analysis of randomized controlled trials. PLoS Med 14:e1002369.

Smith RV, Havens JR, Walsh SL (2016) Gabapentin misuse, abuse and diversion: a systematic review. Addiction 111:1160–1174.

Spoedlin J, Layton JB, Mundkur M, Meier C, Jick SS, Meier CR (2016) The risk of Achilles or biceps tendon rupture in new statin users: a propensity score-matched sequential cohort study. Drug Saf 39:1229–1237.

Steinman MA, Bero LA, Chren MM, Landefeld CS (2006) Narrative review: the promotion of gabapentin: an analysis of internal industry documents. Ann Intern Med 145:284–293.

Thayagarajan V, Su S, Gee J, Duffy J, McCarthy NL, Chan KA, Weintraub ES, Lin ND (2013) Identification of seizures among adults and children following influenza vaccination using health insurance claims data. Vaccine 31:5997–6002.

Wang J, Zhu Y (2017) Different doses of gabapentin formulations for postherpetic neuralgia: a systematical review and meta-analysis of randomized controlled trials. J Dermatol Treat 28:65–77.

Willef PJ, Derry S, Bell RF, Rice AS, Tolle TR, Phillips T, Moore RA (2017) Gabapentin for chronic neuropathic pain in adults. Cochrane Database Syst Rev 6:CD007938.

Womack JA, Goulet JL, Gibert C, Brandt C, Chang CC, Gulanski B, Fraenkel L, Mattocks K, Rimland D, Rodriguez-Barradas MC, Tate J, Yin MT, Justice AC, Veterans Aging Cohort Study Project Team (2011) Increased risk of fragility fractures among HIV infected compared to uninfected male veterans. PLoS One 6:e17217.

Young BA, Lin E, von Korff M, Simon G, Ciechanowski P, Ludman EJ, Eversen-Stewart S, Kinder L, Oliver M, Boyko EJ, Katon WJ (2008) Diabetes complications severity index and risk of mortality, hospitalization, and healthcare utilization. Am J Manag Care 14:15–23.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 Distribution of baseline characteristics in gabapentin exposed patients who did and did not propensity score (PS) match.