Title: Association between gabapentin receipt for any indication and AUDIT-C scores among clinical sub-populations with and without alcohol use disorder

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ABSTRACT (249/250 words)

Background: Current medications for alcohol use disorder (AUD) have limited efficacy and utilization. Some clinical trials have shown efficacy for gabapentin among treatment-seeking individuals. The impact of gabapentin on alcohol consumption in a more general sample remains unknown.

Methods: We identified patients prescribed gabapentin for ≥180 consecutive days for any clinical indication other than substance use treatment between 2009 and 2015 in the Veterans Aging Cohort Study. We propensity-score matched each gabapentin exposed patient with up to five unexposed patients. Multivariable difference-in-difference (DiD) linear regression models estimated the differential change in Alcohol Use Disorders Identification Test – Consumption (AUDIT-C) scores during follow-up between exposed and unexposed patients, by baseline level of alcohol consumption, and daily gabapentin dose. Analyses were stratified by AUD history. Clinically meaningful changes were *a priori* considered a DiD ≥1 point.

Results: Among patients with AUD, AUDIT-C scores decreased 0.39 points (95% CI 0.05, 0.73) more among exposed than unexposed patients ($p<0.03$). Potentially clinically meaningful differences were observed among those with AUD and exposed to ≥1,500 milligrams/day (DiD 0.77, 95% CI 0.15, 1.38; $p<0.02$). No statistically significant effects were found among patients with AUD at doses lower than 1,500 mg/day or baseline AUDIT-C ≥4. Among patients without AUD, we found no overall difference in changes in AUDIT-C scores, nor in analyses stratified by baseline level of alcohol consumption.

Conclusions: Patients exposed to doses of gabapentin consistent with those used in clinical trials, particularly those with AUD, experienced a greater decrease in AUDIT-C scores than matched unexposed patients.

Keywords (4/5): gabapentin, alcohol use disorder, electronic health records, propensity score

INTRODUCTION

Medications and counselling, although underused, are the most effective treatments for patients with alcohol use disorder (AUD) (Jonas et al., 2014, Magill et al., 2015). The efficacy of the three current medications approved by the U.S. Food and Drug Administration (FDA) for the treatment of AUD (i.e., naltrexone, acamprosate, and disulfiram) is limited (Lyon, 2017, Winslow et al., 2016, Litten et al., 2016a, Kranzler and Soyka, 2018), and novel strategies are actively being investigated (Koob and Mason, 2016, Koob and Volkow, 2016, Litten et al., 2016a). This has led researchers to assess the impact of a range of medications approved by the FDA for other indications on alcohol use, including topiramate, varenicline, baclofen, and gabapentin (Litten et al., 2016b, Soyka and Muller, 2017, Kranzler and Soyka, 2018).

Gabapentin, a structural analogue to gamma-aminobutyric acid (GABA), is FDA approved for treatment of partial seizure and postherpetic neuralgia and has shown some efficacy for treatment of AUD in treatment-seeking individuals (Falk et al., 2018, Mason et al., 2014). Anticonvulsants such as gabapentin are believed to decrease craving and alter the subjective effects of alcohol leading to decreased risk of relapse (Pani et al., 2014), although the mechanisms of action are not completely elucidated. A Cochrane Collaborative meta-analysis of three efficacy trials comparing gabapentin to placebo demonstrated that gabapentin use was associated with greater abstinence (decreased drinking days), and reduced heavy drinking, although it had no impact on percent days abstinent or craving (Pani et al., 2014). One efficacy trial comparing gabapentin to placebo demonstrated a dose-response effect on drinking outcomes

among patients with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) alcohol dependence (American Psychiatric Association, 1994). In the 12-week trial, abstinence was 4% with placebo, 11% with 900 milligrams (mg) daily dose of gabapentin, and 17% with 1800 mg/day (p=0.04 for linear dose effect) (Mason et al., 2014). Similar benefits were seen for no heavy drinking and craving (Mason et al., 2014). These results support further evaluation of gabapentin among diverse patient populations.

FDA-approved medications for treatment of AUD are underused by specialists and generalist (e.g. primary care) providers (Finlay et al., 2017, Ford et al., 2017, Lee et al., 2015, Owens et al., 2018, Jonas et al., 2014, Mark et al., 2015, Mark et al., 2009, Mark et al., 2003a, Cohen et al., 2007, Williams et al., 2017, Harris et al., 2010, Harris et al., 2012). Limited efficacy, low patient demand, formulary restrictions, and lack of experience with these medications for AUD treatment are known concerns among providers (Mark et al., 2009, Mark et al., 2003a, Mark et al., 2003b, Williams et al., 2018, Harris et al., 2013). However, a potential advantage of gabapentin for treatment of AUD is that it is commonly prescribed “off-label” for peripheral neuropathy, fibromyalgia, and other painful conditions (Shanthanna et al., 2017, Kesselheim et al., 2011), which suggests that clinicians have a level of comfort and familiarity with its use.

The impact of gabapentin on alcohol consumption when prescribed for indications other than treatment of AUD is unknown. Previous work has demonstrated that lower levels of alcohol exposure are associated with greater risk of physiologic injury and mortality

among HIV-infected patients compared to uninfected patients (Justice et al., 2016) and low levels of alcohol negatively impacts prognosis in a range of medical conditions such as depression and liver disease (Sullivan et al., 2011, Sullivan et al., 2005, Lim et al., 2014). Therefore, we sought to determine the impact of gabapentin on changes in alcohol use among patients receiving gabapentin for common medical conditions, who reported any alcohol consumption and whether effects differed by AUD history, baseline level of alcohol consumption, and prescribed daily dose of gabapentin. We hypothesized that the effect of gabapentin on alcohol consumption would be greater among those with AUD, higher baseline levels of alcohol consumption, and prescribed higher doses.

MATERIALS AND METHODS

Study population

We used data from the Veterans Aging Cohort Study (VACS), which has been described in detail (Fultz et al., 2006, Justice et al., 2006). Briefly, VACS is a large observational cohort based on data from the national Veterans Health Administration (VA) electronic health records (EHR) that includes all HIV-infected patients in VA care (>50,000 HIV+ subjects) and uninfected patients (>100,000) 1:2 matched on region, age, race/ethnicity, and sex. VACS 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.

For this analysis, we included HIV+ and HIV-uninfected patients who did (gabapentin exposed) and did not (gabapentin unexposed) receive gabapentin dispensed at VA pharmacies. For the gabapentin exposed group, we included all patients who received gabapentin for at least 180 continuous days for any indication between 1 January 2009 and 30 September 2015 from the following VA clinics: primary care, infectious disease, neurology, general internal medicine, physical medicine and rehabilitation services, pain, podiatry, orthopedics, women's clinic, 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. Importantly, we did not include patients with gabapentin prescriptions from substance use treatment programs; however, we did not exclude patients who subsequently visited a substance use treatment program during follow-up.

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 utilized a 12-month washout period to identify new episodes of gabapentin exposure. Therefore, patients who received gabapentin in 2008 were only eligible to be followed after a one-year period of no gabapentin exposure. We excluded patients who had no outpatient care in the VA in the year prior to their index date and those who had no measurement of alcohol consumption in the two years prior to their

index date. We also excluded patients who reported no alcohol consumption based on the closest measurement to baseline.

Propensity score model and matching

To address concerns of confounding by indication, whereby patients with specific alcohol consumption patterns might be more likely to receive gabapentin, we generated propensity scores. Propensity scores are used to adjust for the conditional probability of being prescribed gabapentin given a set of covariates that are associated with both gabapentin receipt and alcohol consumption or associated with alcohol consumption only (Brookhart et al., 2006). Matching by propensity score provides a means to balanced exposure groups similar to random treatment allocation in a randomized controlled trial (Austin, 2011). We hypothesized that the effects of gabapentin on alcohol consumption may differ in patients with and without diagnosed AUD prior to their index date. Therefore, propensity scores (i.e. the predicted probability of gabapentin exposure) were estimated using separate multivariable logistic regression models for patients with and without AUD at baseline, as defined below. Estimating propensity scores separately has been shown to be unbiased, particularly in subgroup analyses with small sample sizes (Eeren et al., 2015, Green and Stuart, 2014, Rassen et al., 2012).

Variables used in the propensity score models were selected a priori based on clinical knowledge (Hernan et al., 2002) and included: year of index date, age at baseline, race, smoking status, body mass index at baseline, site prescribing pattern (the proportion of

patients who initiated gabapentin stratified by year and HIV status), lab values closest to the index date (including haemoglobin, international normalized ratio, triglycerides, CD4 cell count), hepatitis C virus (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, post-traumatic 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 lab, 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 (starting on or elapsing baseline) to treat pain (including non-steroidal anti-inflammatory drugs (NSAIDs), opioids, muscle relaxants, and antidepressants) and seizures were included in the model. Interaction terms were explored for significance, and six were kept in the final model (all $p<0.05$). The model c-statistic was 0.83 for patients with AUD and 0.84 in patients without AUD, indicating

adequate discrimination between gabapentin exposed and unexposed patients in both models (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 non-exchangeable unexposed patients (Figure 1) (Spoendlin et al., 2016). We conducted propensity score matching within pre-specified subgroups of patients based on baseline Alcohol Use Disorders Identification Test – Consumption (AUDIT-C) scores and aggregated these subgroup strata to create the full matched cohort (Wang et al., 2018). Each exposed patient was matched to up to five unexposed patients with index dates in the same calendar year, using a greedy matching algorithm (Cormen, 2009).

Measures and follow-up

Baseline AUD was determined by one inpatient or two outpatient ICD-9 codes (303.X or 305-305.03) at any time prior to baseline. Alcohol consumption was assessed using the AUDIT-C, a three-question self-report alcohol screening questionnaire that detects heavy drinking and/or active AUD (Bush et al., 1998, Fiellin et al., 2000). AUDIT-C scores range from 0-12 with the likelihood of physiologic injury and mortality increasing as AUDIT-C scores increase (Justice et al., 2016). An AUDIT-C score of zero is defined as no current alcohol use, 1-3 suggests lower-risk drinking, 4-7 suggests at-risk drinking, and ≥8 suggest hazardous or heavy episodic alcohol consumption. Since 2007, the VA has required annual AUDIT-C screening on all patients in primary care (Bradley et al., 2006).

All patients were followed from their index date for a maximum of two years or until their last VA visit or death. Additionally, gabapentin exposed patients were censored at 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

All statistical analyses were performed separately for patients with and without AUD at baseline. While evidence of alcohol consumption at baseline as measured by the AUDIT-C was a criterion for study inclusion, we did not restrict matching eligibility on the availability of a follow-up AUDIT-C (the outcome) as such a restriction would not be available at baseline in an analogous randomized clinical trial. Thus, 1,119 (44%) exposed patients in the propensity score matched sample did not have a follow-up AUDIT-C and were unable to be included in regression models. If an exposed patient did not have a follow-up AUDIT-C, we removed their entire matched set of unexposed patients to maintain a balanced sample. If an unexposed patient did not have a follow-up AUDIT-C, we kept the remaining patients in their matched set in the analytic sample as long as there was another unexposed patient in the set. We used chi-square tests to examine balance between exposed and unexposed patients included in the full sample, propensity-score matched sample, and final analytic sample.

Among those in the final analytic sample, we calculated the average pre- and post-index AUDIT-C scores. Pre-index AUDIT-C scores were defined as the closest on or before the index date, within a maximum of two years. Post-index AUDIT-C scores were defined as the closest measure to the end of exposure or within 30 days of end of follow-up. We then used multivariable difference-in-difference (DiD) linear regression models (Donald and Lang, 2007, Lechner, 2011) to estimate the differential change between pre- and post-index AUDIT-C scores. We *a priori* considered a DiD estimate ≥1 point clinically meaningful (Rubinsky et al., 2013). To account for residual confounding not captured by propensity score matching, models were adjusted for any characteristic shown to be unbalanced between exposed and unexposed patients in addition to age, total number of medications prescribed during follow-up, and VACS Index. The VACS Index – a measure of physiologic injury incorporating age, CD4 count, HIV-1 RNA, hemoglobin, a marker of liver fibrosis (FIB-4), estimated glomerular filtration rate (eGFR), and HCV status – has been shown to predict acquired immunodeficiency syndrome (AIDS) and non-AIDS morbidity and mortality in multiple settings (Akgun et al., 2013, Akgun et al., 2014, Escota et al., 2015, Justice et al., 2013, Marquine et al., 2014, Tate et al., 2013, Womack et al., 2013).

We also performed subgroup analyses by self-reported level of alcohol consumption at baseline (as determined by AUDIT-C) and average daily gabapentin dose during follow-up. Daily dose was categorized to include roughly equal numbers of patients in each group: low (<600 milligrams [mg]), medium (600 mg-1,499 mg), and high (≥1,500 mg). Lastly, we conducted a sensitivity analysis excluding patients with a visit to a substance

use treatment program during follow-up. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Sample

We identified 5,721 gabapentin exposed patients and 52,243 gabapentin unexposed patients who reported any alcohol consumption in the two years prior to their index date. A total 2,520 exposed patients were matched (Supplemental Table 1); however, 1,119 (44%) did not have a follow-up AUDIT-C and were unable to be included in analysis. Among those with AUD in the final analytic sample, 29 (5.2%) were matched to five unexposed patients, 55 (9.8%) to four, 86 (15.3%) to three, 121 (21.5%) to two, and 271 (48.2%) to one unexposed patient. Among patients without AUD, 87 (10.4%) were matched to five unexposed patients, 125 (14.9%) to four, 124 (14.8%) to three, 167 (19.9%) to two, and 336 (40.0%) to one unexposed patient. Thus, the final analytic sample consisted of 562 exposed and 1,136 unexposed patients with AUD, and 839 exposed and 1,977 unexposed patients without AUD.

Prior to propensity score matching, the distribution of baseline characteristics significantly differed between gabapentin exposed and unexposed patients with or without AUD (Table 1). In the final analytic sample, gabapentin exposed and unexposed patients with or without AUD were well balanced (Table 1). There was a statistically significant difference in the proportion of antidepressant prescriptions at baseline among

patients with AUD and the proportion of neuropathic pain diagnoses among patients without AUD. These covariates were included in adjusted models.

Gabapentin exposed patients who were not matched had higher propensity scores than those who were matched (median 0.23, interquartile range [IQR] 0.12-0.43 not matched; median 0.05, IQR 0.03-0.08 matched). Median follow-up time was 334 days (IQR 237-475 days) for patients with AUD and 385 days (IQR 266-574 days) for patients without AUD. Among exposed patients in the final sample, 31% were prescribed daily doses of gabapentin <600 mg, 44% were prescribed between 600-1,500 mg, and 25% were prescribed ≥1,500 mg.

Changes in AUDIT-C scores

There was no difference in the distribution of time between post-index AUDIT-C measures and end of follow-up between exposed and unexposed patients (Kruskal-Wallis p=0.11). Median difference between end of follow-up and post-index AUDIT-C was 106 days (IQR 30-195 days).

Overall, AUDIT-C scores decreased during the study period regardless of AUD history, baseline AUDIT-C, or gabapentin dose. Among patients with AUD, average AUDIT-C scores decreased from 4.16 (standard deviation [SD] 0.13) to 3.15 (SD 0.13) among exposed patients and 3.94 (SD 0.10) to 3.32 (SD 0.10) among unexposed patients (Table 2). The adjusted DiD estimate was statistically significant but the confidence interval did not include our *a priori* threshold for a clinically meaningful difference (DiD

0.39 points, 95% confidence interval [CI] 0.05, 0.73; p=0.0264). In analysis stratified by baseline AUDIT-C and among those with AUDIT-C of 1-3, average scores decreased 0.03 points among exposed and increased 0.57 points among unexposed patients (DiD 0.59, 95% CI 0.20, 0.99; p=0.0032). No significant differences were observed for higher baseline AUDIT-C. The largest DiD estimate was seen among patients with AUD at baseline and exposed to ≥1,500 mg/day of gabapentin (DiD 0.77 points, 95% CI 0.15, 1.38; p=0.0149), which was statistically significant and the confidence interval included our criteria for a clinically meaningful difference.

Patients without AUD had lower pre-index AUDIT-C scores and smaller decreases in AUDIT-C scores. Average AUDIT-C scores decreased from 2.61 (SD 0.07) to 2.02 (SD 0.07) among exposed patients and 2.49 (SD 0.05) to 2.05 (SD 0.05) among unexposed patients (Table 2). The adjusted DiD estimate was not statistically significant (DiD 0.14, 95% CI -0.01, 0.30; p=0.0691) (Table 2). The only statistically significant DiD estimate among patients without AUD was among those exposed to <600 mg/day of gabapentin (DiD 0.37 points, 95% CI 0.12, 0.61; p=0.0034), but this was not clinically meaningful. In sensitivity analyses excluding patients with a visit to a substance use treatment program during follow-up, DiD estimates were of a similar magnitude and direction although with wider confidence intervals due to smaller sample sizes (Supplemental Table 2).

DISCUSSION

This propensity-score matched analysis of the association between gabapentin use, prescribed for any indication, and patients' reported alcohol consumption found an

overall statistically significant but not clinically meaningful difference in changes in AUDIT-C scores among patients with AUD. Analyses restricted to patients with AUD and exposed to ≥1,500 mg/day of gabapentin suggested a statistically significant and potentially clinically meaningful decrease in reported alcohol consumption. No other statistically significant effects were found among patients with AUD at doses lower than 1,500 mg/day. Interestingly, analyses among patients with AUD who reported low levels of alcohol consumption at baseline demonstrated no change in alcohol consumption among exposed and an increase in alcohol consumption among unexposed, resulting in a statistically significant DiD estimate. No other statistically significant effects were found among patients with AUD at doses lower than 1,500 mg/day or baseline AUDIT-C ≥4.

Among patients without AUD, we found no overall difference in changes in AUDIT-C scores, nor in analyses stratified by baseline level of alcohol consumption. While no effect was found among patients without AUD at doses ≥600 mg/day, analyses restricted to those prescribed <600 mg/day demonstrated a statistically significant but not clinically meaningful difference in changes in reported alcohol use. As shown in Table 2, this association was driven by an increase in reported alcohol consumption among unexposed patients and not a decrease among exposed patients.

One efficacy study evaluated the impact of gabapentin dose on alcohol-related outcomes. This randomized clinical trial, with a high dropout rate (43%, 65/150), noted a dose-response effect with improved outcomes at 1800 mg/day compared with placebo

and 900 mg/day (Mason et al., 2014). Investigators chose these doses based on FDA-approved dose ranges for seizure and neuropathic pain. Our findings also demonstrate a greater impact of gabapentin at higher doses, which we defined as ≥1500 mg/day because we were not powered to limit to ≥1800 mg/day. Preliminary findings from another recent efficacy trial of a prodrug formulation of gabapentin, called gabapentin enacarbil, found no effect of any drinking measure among 346 patients with moderate or severe AUD (Falk et al., 2018). However, Falk et al suggest these results may be partially explained by the differential FDA-approved dosage of gabapentin and gabapentin enacarbil. The mechanism of action for gabapentin in the treatment of unhealthy alcohol use is not completely understood. Its activity is presumably related to the ability to increase or modulate GABA activity via voltage dependent calcium channels and direct synthesis (Leung et al., 2015). Its clinical anxiolytic and sedative effects may address withdrawal and craving in a dose-dependent manner among those with AUD. The impact of gabapentin on craving, however, is not clear (Pani et al., 2014).

This research differs from recent efficacy studies of the impact of gabapentin on alcohol consumption in a number of important ways. First, we evaluated the impact of gabapentin on alcohol consumption in a real-world setting among patients who did not receive their gabapentin prescription via a substance use treatment program. We addressed methodological challenges inherent to observational study designs by using 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. Second, previous studies have shown that motivation to receive treatment for AUD can impact treatment outcomes (DiClemente et al., 2017, DiClemente et al., 2004, Field et al., 2009). Given that patients in our sample were prescribed gabapentin from non-substance use treatment providers, it is likely that patients were not receiving gabapentin to address their alcohol use. Nonetheless, more than one-third of exposed and unexposed patients with AUD were seen in a substance use treatment program during follow up. Findings from sensitivity analyses excluding patients with a visit to a substance use treatment program were largely consistent with our primary findings, though with less precision given the smaller sample sizes. Therefore, our findings may underestimate the impact of gabapentin in those who might be more motivated to treat their AUD. Third, we determined the association between gabapentin exposure and alcohol use in patients with any level of alcohol consumption. Decreasing alcohol consumption in patient populations who do not meet formal criteria for unhealthy alcohol use or AUD might result in improvement of other conditions such as HIV, depression and liver fibrosis (Lim et al., 2014, Sullivan et al., 2005, Sullivan et al., 2011, Justice et al., 2016). One of the advantages of using real-world, observational data to examine the impact of gabapentin exposure on alcohol consumption is the ability to determine whether an effect exists across a wide range of drinking behaviors. Some patients in our study who reported unhealthy alcohol use did not have diagnosed AUD, and notably gabapentin did not seem to have a clinically meaningful impact on their AUDIT-C scores.

There are limitations to our work. First, our sample was restricted to U.S. Veterans who were receiving care in the VA healthcare system, so our findings may not generalize to Veterans who did not receive care in the VA or to other patient populations. Second, due to the VACS sampling strategy and characteristics of the Veteran population, our sample was enriched with older men and patients with multiple medical comorbidities including HIV infection, which reflects a segment of patients aging with HIV disease but may not generalize to other clinical settings. Compared to estimates from the Veteran Population Projection Model 2016, our analytic sample accurately represented Veterans aged 60+, under represented younger Veterans, and somewhat over represented middle-aged Veterans. With respect to race/ethnicity, our sample over represented black Veterans. Third, AUDIT-C scores were collected as part of routine clinical care and may not reflect actual drinking patterns (Williams et al., 2015, McGinnis et al., 2016, Bradley et al., 2011). Finally, some of our analyses lacked adequate power due to small samples in certain patient subgroups. Nonetheless, we believe our findings from a large national integrated health care system provide novel information on the impact of gabapentin on alcohol use in individuals who may or may not have been receiving treatment for substance use.

This work has important implications for researchers and clinicians. We have used real-world data to demonstrate that gabapentin exposure of at least 180 consecutive days at doses <1,500 mg/day was not associated with a decrease in self-reported alcohol consumption among patients receiving gabapentin but not as treatment for their drinking. We did observe a potential threshold effect ≥1,500 mg/day among patients

with diagnosed AUD, which is consistent with the dose response seen in a prior clinical trial (Mason et al., 2014). This finding suggests the impact on drinking outcomes may not be present at lower doses and may be related to the medication's mechanism of action. Our selection of patients who had ≥180 consecutive days of gabapentin exposure reflects considerable stability and the impact of gabapentin on alcohol consumption may differ at shorter exposures. In addition to consideration of gabapentin dose and duration, it is important to recognize that since the gabapentin was provided by clinicians outside of substance use treatment programs, our findings were most commonly observed in the absence of counselling. Additional research that pairs information and/or motivational efforts targeted to address alcohol consumption among patients receiving gabapentin in general medical settings may be warranted.

In contrast to the limited use of FDA-approved medications to treat AUD, the widespread prescribing of gabapentin for other conditions indicates that many clinicians are familiar with it, which makes it a potentially useful addition to the array of medications available to treat AUD. However, emerging data indicates that gabapentin can be used non-medically for euphoria among certain patient subgroups (Peckham et al., 2017, Smith et al., 2016). Clinicians prescribing gabapentin will need to use caution to monitor patients for evidence of non-medical use or diversion of gabapentin. In addition, adverse effects known to be associated with gabapentin warrant evaluation in potentially vulnerable patient subgroups including those with HIV and HCV. Our findings indicate that future clinical trials should evaluate the impact of gabapentin on alcohol

use in wider patient populations including non-treatment seeking patients with and without AUD.

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FIGURE LEGENDS

Figure 1. Distribution of propensity scores in gabapentin exposed and unexposed patients in the full cohort before matching, by alcohol use disorder (AUD) history

Panel **a** title: Prior AUD

Panel **b** title: No prior AUD

Figure 2. Difference-in-difference estimates and 95% confidence intervals of self-reported changes in AUDIT-C scores associated with gabapentin exposure among non-treatment seeking patients and their propensity-score matched controls, by AUD history, baseline AUDIT-C, and prescribed dose of gabapentin

Notes: ** for $p<0.05$, * for $p<0.10$; Difference-in-difference = reported AUDIT-C decrease among gabapentin exposed patients minus reported AUDIT-C decrease among propensity-score matched unexposed patients

Abbreviations: AUDIT-C - Alcohol Use Disorders Identification Test – Consumption; AUD – alcohol use disorder; mg - milligrams

Figure 1. Distribution of propensity scores in gabapentin exposed and unexposed patients in the full cohort before matching, by alcohol use disorder (AUD) history

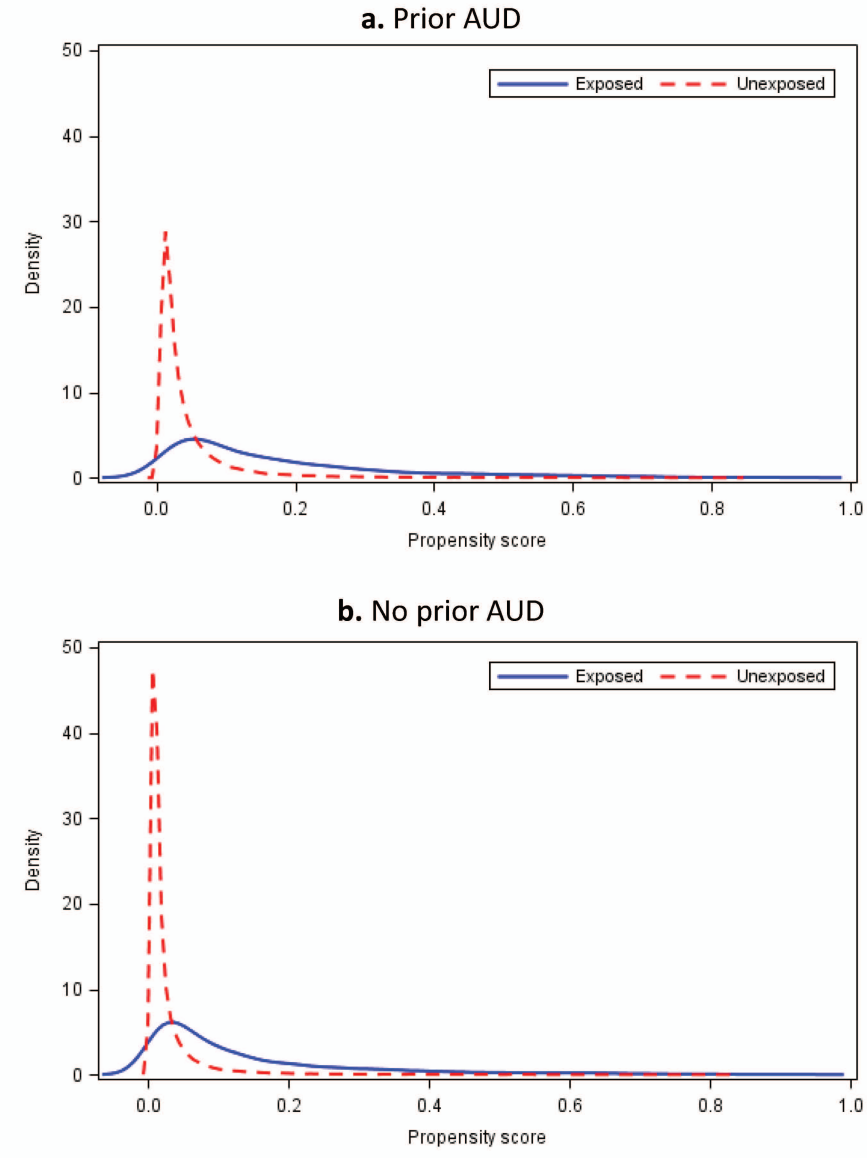
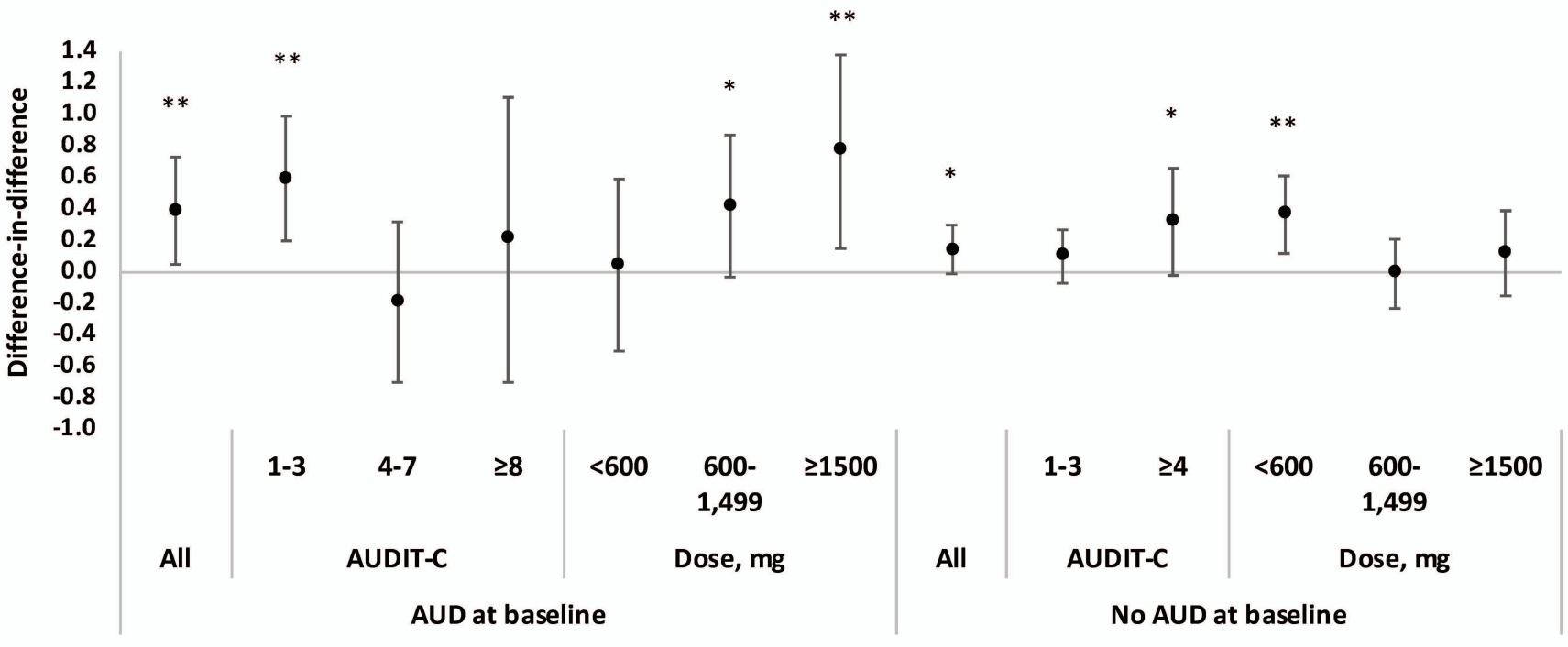


Figure 2. Difference-in-difference estimates and 95% confidence intervals of self-reported changes in AUDIT-C scores associated with gabapentin exposure among non-treatment seeking patients and their propensity-score matched controls, by AUD history, baseline AUDIT-C, and prescribed dose of gabapentin



Notes: ** for p<0.05, * for p<0.10; Difference-in-difference = reported change in AUDIT-C among gabapentin exposed patients minus reported change in AUDIT-C among propensity-score matched unexposed patients

Abbreviations: AUDIT-C - Alcohol Use Disorders Identification Test – Consumption; AUD – alcohol use disorder; mg - milligrams

Supplemental Table 1. Distribution of baseline characteristics in the full propensity score (PS)-matched sample irrespective of available follow-up AUDIT-C, by history of AUD at baseline

	AUD		No AUD	
	Exposed	Unexposed	Exposed	Unexposed
Characteristic	**n=1,069**	**n=1,069***	**n=1,451**	**n=1,451***
Age				
20-44	121 (11.3)	119 (11.1)	198 (13.7)	256 (17.6)
45-54	118 (11.0)	94 (8.8)	194 (13.4)	181 (12.5)
55-59	222 (20.8)	228 (21.4)	247 (17.0)	234 (16.1)
60+	608 (56.9)	628 (58.8)	812 (56.0)	780 (53.8)
Race				
Black	573 (53.6)	576 (53.9)	547 (37.7)	590 (40.7)
White	393 (36.8)	382 (35.7)	732 (50.5)	688 (47.4)
Hispanic	77 (7.2)	87 (8.2)	106 (7.3)	122 (8.4)
Other	26 (2.4)	24 (2.2)	66 (4.6)	51 (3.5)
Sex				
Male	1,048 (98.0)	1,054 (98.6)	1,384 (95.4)	1,400 (96.5)
Any hospitalization	48 (4.5)	44 (4.2)	40 (2.8)	29 (2.0)
HIV/HCV infection				
Uninfected	647 (60.5)	651 (60.9)	951 (65.5)	983 (67.8)
HCV mono-infected	131 (12.3)	147 (13.7)	29 (2.0)	35 (2.4)
HIV mono-infected	202 (18.9)	197 (18.5)	423 (29.2)	394 (27.1)
HIV/HCV co-infected	89 (8.3)	74 (6.9)	48 (3.3)	39 (2.7)
Conditions				
Seizure	108 (10.1)	105 (9.8)	69 (4.8)	71 (4.9)
Diabetes	255 (23.9)	261 (24.4)	428 (29.5)	388 (26.7)
Neuropathic pain	207 (19.4)	177 (16.5)	371 (25.6)	283 (19.5)
Any chronic pain	1,051 (98.3)	1,051 (98.3)	1,380 (95.1)	1,393 (96.0)
Other prescription				
Opioid	261 (24.4)	237 (22.2)	349 (24.1)	352 (24.3)
Antidepressant	68 (6.4)	46 (4.3)	104 (7.2)	73 (5.1)
NSAID	469 (43.9)	485 (45.3)	592 (40.8)	601 (41.5)
Muscle relaxant	94 (8.8)	87 (8.2)	121 (8.3)	128 (8.8)
Anticonvulsant	55 (5.1)	43 (4.1)	45 (3.1)	37 (2.5)
Visit to substance use treatment program during follow-up	419 (39.2)	358 (33.5)	34 (2.3)	25 (1.7)

Notes: some PS-matched patients did not have an outcome measurement and could not be modeled; all statistics reported as n (%); up to five unexposed patients were matched to each exposed patient; *unexposed matches were weighted according to number of matches; tests for signficance were conducted with chi-square tests

Abbreviations: PS - propensity score; AUDIT-C - Alcohol Use Disorders Identification Test – Consumption; HIV - human immunodeficiency virus; HCV - hepatitis C virus; AUD - alcohol use disorder; NSAID - non-steroidal anti-inflammatory drug

Supplemental Table 2. Sensitivity analysis comparing the final model from the primary analysis to a model restricted to patients without a substance use treatment program visit during follow-up among those with alcohol use disorder (AUD)

		Primary analysis, all AUD		Restricted to those w/o SUD visit	
		Exposed	Unexposed	Exposed	Unexposed
		n=562	n=1,136	n=338	n=709
All patients	**Pre**	4.16 (0.13)	3.94 (0.10)	3.21 (0.16)	3.23 (0.11)
	Post	3.15 (0.13)	3.32 (0.10)	2.60 (0.16)	2.93 (0.11)
	D^n	-1.01 (0.14)	-0.62 (0.10)	-0.61 (0.18)	-0.30 (0.12)
	DiD (95% CI)	0.39 (0.05, 0.73), p=0.0264		0.31 (-0.11, 0.73), p=0.1483	
By baseline AUDIT-C					
		n=310	**n=649**	**n=221**	**n=469**
1-3	**Pre**	2.18 (0.13)	2.19 (0.09)	2.20 (0.15)	2.19 (0.10)
	Post	2.16 (0.13)	2.75 (0.09)	2.28 (0.15)	2.63 (0.10)
	D^n	-0.03 (0.17)	0.57 (0.11)	0.08 (0.19)	0.44 (0.13)
	DiD (95% CI)	0.59 (0.20, 0.99), p=0.0032		0.36 (-0.09, 0.81), p=0.1131	
		n=189	**n=378**	**n=99**	**n=199**
4-7	**Pre**	5.29 (0.16)	5.18 (0.12)	5.28 (0.24)	5.04 (0.15)
	Post	4.12 (0.16)	3.82 (0.12)	3.52 (0.24)	3.56 (0.15)
	D^n	-1.17 (0.21)	-1.37 (0.15)	-1.75 (0.31)	-1.48 (0.19)
	DiD (95% CI)	-0.19 (-0.70, 0.32), p=0.4636		0.27 (-0.45, 0.99), p=0.4593	
		n=63	**n=109**		
≥8	**Pre**	10.03 (0.27)	9.89 (0.21)		
	Post	4.69 (0.27)	4.76 (0.21)	[§]	
	D^n	-5.33 (0.37)	-5.12 (0.28)		
	DiD (95% CI)	0.21 (-0.70, 1.11), p=0.6500			
By average dose, mg					
		n=168	**n=1,136**	**n=109**	**n=709**
<600	**Pre**	3.78 (0.22)	3.95 (0.10)	3.11 (0.27)	3.23 (0.11)
	Post	3.11 (0.22)	3.32 (0.10)	2.68 (0.27)	2.93 (0.11)
	D^n	-0.67 (0.26)	-0.62 (0.10)	-0.43 (0.33)	-0.30 (0.12)
	DiD (95% CI)	0.05 (-0.50, 0.59), p=0.8650		0.13 (-0.55, 0.81), p=0.7106	
		n=267	**n=1,136**	**n=151**	**n=709**
600-1,499	**Pre**	4.25 (0.18)	3.95 (0.10)	3.13 (0.22)	3.23 (0.11)
	Post	3.21 (0.18)	3.32 (0.10)	2.45 (0.22)	2.93 (0.11)
	D^n	-1.04 (0.21)	-0.62 (0.10)	-0.68 (0.26)	-0.30 (0.12)
	DiD (95% CI)	0.42 (-0.03, 0.87), p=0.0685		0.38 (-0.18, 0.94), p=0.1800	
		n=127	**n=1,136**	**n=78**	**n=709**
≥1,500	**Pre**	4.47 (0.26)	3.95 (0.10)	3.52 (0.31)	3.23 (0.11)
	Post	3.08 (0.26)	3.32 (0.10)	2.82 (0.31)	2.93 (0.11)
	D^n	-1.39 (0.30)	-0.62 (0.10)	-0.69 (0.38)	-0.30 (0.12)
	DiD (95% CI)	0.77 (0.15, 1.38), p=0.0149		0.40 (-0.38, 1.18), p=0.3156	

Abbreviations: AUDIT-C - Alcohol Use Disorders Identification Test - Consumption; Pre - pre-index AUDIT-C score; Post - post-index AUDIT-C score; D^n - change in AUDIT-C score; DiD - difference-in-difference estimate; CI - confidence interval

Notes: statistics reported as mean (standard error)

[§]Too few patients for model to converge among patients with AUDIT-C ≥8 after restricting