GABAergic but not Antidepressant Medications Increase Risk for *Clostridioides difficile* Infection in a National Cohort of Veterans

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**Background.** *Clostridioides difficile* infection (CDI) is primarily mediated by alterations in the host gut ecosystem. While antibiotic use is the primary risk factor for CDI, other medications that modulate the gut ecosystem, particularly those targeting the gut–brain axis, could impact CDI risk. This study aimed to investigate the association between recent antidepressant and gamma-aminobutyric acid (GABA)–ergic medication use with CDI risk in a national cohort of United States veterans.

**Methods.** This was a retrospective case–control study of patients seen in Veterans Health Administration facilities from October 2002 to September 2014. CDI and non-CDI control patients were propensity score matched 1:1 using a maximum caliper of 0.0001. Antidepressant and GABAergic medication use 90 days before cohort inclusion were analyzed for CDI association using bivariable and multivariable logistic regression models.

**Results.** A total of 85,831 patients were included, and 9,287 CDI and 9,287 control patients were propensity score matched. Antidepressant use overall was not significantly associated with CDI risk (odds ratio [OR], 1.05; 95% CI, 0.98–1.12), although GABAergic medication use was associated with increased risk (OR, 1.81; 95% CI, 1.70–1.92). In multivariable models of individual medications/classes, benzodiazepines had the strongest CDI association (OR, 1.91; 95% CI, 1.77–2.07). SSRIs (OR, 0.88; 95% CI, 0.81–0.95) and bupropion (OR, 0.67; 95% CI, 0.57–0.78) were negatively associated with CDI.

**Conclusions.** In this national study of veterans, GABAergic medication use was a positive predictor of CDI risk, though antidepressant use was not. Further research is needed to understand biological mechanisms, and confirmatory studies are needed to validate these findings.

**Keywords.** GABA modulators; antidepressants; *Clostridioides difficile* infection risk.

*Clostridioides difficile* infection (CDI) continues to be an important source of morbidity and mortality in United States, affecting nearly half a million American inpatients and outpatients annually [1, 2]. The pathogenesis of CDI is mediated by disruption of the commensal gut microbiota, which results in a loss of colonization resistance [3]. Antibiotics are considered the primary risk factor for CDI due to alteration of the gut ecosystem (ie, dysbiosis) favoring *C. difficile* colonization and growth [4, 5]. Presumably, other medications that modulate the gut ecosystem could increase CDI risk.

The gut–brain axis is a bidirectional relationship between the central and enteric nervous systems and intestinal functions [6, 7]. The gut microbiota and the brain communicate with each other via neural, endocrine, immune, and humoral links [6, 7]. There are a number of bacterial taxa that play a role in the regulation of metabolites and neurotransmitters. Specifically, the gut microbiota produce tryptophan, a precursor to serotonin and indole, the latter of which has been shown to predispose patients to developing behavioral changes, like anxiety and depression [7]. Interestingly, selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants have antimicrobial activity, which could impact the gut's ability to prevent *C. difficile* colonization and infection. Another neurotransmitter produced by the gut microbiota includes gamma-aminobutyric acid (GABA), a major neurotransmitter in the central nervous system that can have modulatory effects on the enteric neurons and immune cells [8, 9]. A recent study found an association between increased GABA levels and CDI disease recurrence, suggesting a possible role for GABA in CDI pathogenesis [10].

Despite the potential risk for CDI with antidepressant and GABAergic medications due to gut microbiota interactions, few studies have evaluated this association clinically. This study sought to quantify the association between antidepressant and...
GABAergic medications with CDI in a national cohort of US veterans.

METHODS

Study Design
This was a case–control study of all patients receiving care at any Veterans Health Administration hospital or clinic in the United States between October 1, 2002, and September 30, 2014. Data were obtained from the VA Informatics and Computing Infrastructure (VINCI), which includes administrative, clinical, laboratory, and pharmacy data repositories that are linked using unique patient identifiers. Data collection was performed at the South Texas Veterans Health Care System, Audie L. Murphy VA Hospital, San Antonio, Texas.

Study Population and Definitions
The patient population for this study has been described previously [11]. In brief, CDI patients included adults who had any inpatient or outpatient International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code for CDI (008.45) plus any positive stool test (eg, toxin enzyme immunoassay, nucleic acid amplification test ± glutamate dehydrogenase test) for CDI during the visit or within 7 days of the visit during the study period and active CDI therapy (oral vancomycin, metronidazole, fidaxomicin, rifaximin, or nitazoxanide). We limited our cohort to first-episode CDI patients only by excluding those patients with an ICD-9-CM code for CDI in the year before study inclusion. The non-CDI control group was created by identifying a random sample of veterans without an ICD-9-CM code for CDI any time during the cohort period. Controls were further limited to group, matched 2:1 with CDI patients, by first calculating the proportion of included CDI patient encounters that were inpatient (~90%), then extracting an approximately equivalent proportion of controls whose encounter was inpatient.

Data collection included patient demographics at the time of cohort inclusion. For these demographics (eg, sex, race, ethnicity), we included a missing category. Other variables that were absent from the medical chart (eg, comorbidities, medications) were assumed to have not occurred. Charlson comorbidities and other relevant diagnoses (as defined by ICD-9-CM codes) were collected in the year before the visit. Prior hospitalization was defined as any inpatient stay in the prior 90 days. Inpatient or outpatient medication use in the 90 days preceding cohort inclusion included non-CDI antibiotics, antidiarrhea medications, bowel prep, gastric acid suppressants, and opioid analgesics. Antidepressant use in the 90 days preceding cohort inclusion was defined as at least 1 outpatient fill or inpatient dose administered of an SSRI, serotonin-norepinephrine reuptake inhibitor (SNRI), bupropion, trazadone, mirtazapine, or tricyclic antidepressant. GABAergic medication use was similarly defined using the following medications: benzodiazepines, eszopiclone, zolpidem, gabapentin, pregabalin, or baclofen. Outpatient medications were identified using the “RxOutput” VINCI file, which includes all VA outpatient filled prescriptions. Inpatient medications were identified using the “BMCAMedicationLog” and “Inpatient Intravenous Medications (IV)” files, which include medications administered to a hospitalized patient.

Statistical Approach
First, all collected variables were presented descriptively and compared between CDI and control groups using the chi-square test for nominal variables and Wilcoxon rank-sum test for continuous variables. Next, we used propensity score matching to generate CDI and control groups that were comparable in baseline characteristics. To do this, we estimated the probability of patients being diagnosed with CDI using a logistic regression model with CDI as the dependent variable and the following independent variables: age, sex, race, ethnicity, fiscal year, prior hospitalization, visit type, 21 comorbidities, and 5 prior medication classes (Table 1). These covariates were chosen to control for the most common risk factors for CDI [4, 5, 12–16]. We nearest-neighbor matched patients 1:1 within a propensity score maximum caliper of 0.0001. This technique has been used previously to match groups in case–control studies [17, 18]. Following propensity score matching, we compared variables between cohorts using appropriate bivariable statistics. We then evaluated the association between antidepressant and GABAergic medication use with CDI in a series of bivariable logistic regression models. Then, we conducted multivariable logistic regression to assess the independent association of each medication/class with CDI using CDI as the dependent variable and the following covariates: SSRIs, SNRIs, bupropion, trazadone, mirtazapine, tricyclic antidepressants, benzodiazepines, gabapentin, and zolpidem. Next, we conducted a subgroup analysis by fiscal year (2003 to 2008 vs 2009 to 2014) to account for changes in CDI diagnostics and medication prescribing practices over time. Finally, to validate the generalizability of our findings, we conducted a multivariable logistic regression analysis using the entire (nonmatched) cohorts to assess the independent association of antidepressant use and GABAergic medication use with CDI using the same 33 covariates used for the propensity score adjustment.

RESULTS
A total of 85 831 patients were included in this study before matching: 26 149 in the CDI cohort and 59 682 in the control cohort. Table 1 lists the baseline characteristics of these patient populations. The patients in the CDI group were predominantly elderly (median age, 67 years), male (95.9%), and White (71.8%). Before matching, there were statistically significant differences between the CDI cohort and the control cohort for all the independent
Table 1. Baseline Characteristics of Unmatched Cohorts and Matched Cohorts

| Characteristic                  | Unmatched Cohorts | Matched Cohorts | PValue | PValue |
|--------------------------------|-------------------|-----------------|--------|--------|
|                               | CDI Group (n = 26149) | Control Group (n = 59682) |        |        |
| Age, median (IQR), y           | 67 (60–78)        | 61 (52–72)      | <.0001 |        |
| Male sex, %                    | 95.9              | 94.3            | <.0001 |        |
| Race, %                        |                   |                 |        |        |
| White                          | 70.2              | 66.8            | <.0001 |        |
| Black                          | 22.0              | 21.9            | 19.4   | 19.3   |
| Other                          | 4.6               | 5.8             | 5.3    | 5.2    |
| Missing                        | 3.2               | 5.5             | 3.7    | 3.3    |
| Ethnicity, %                   |                   |                 | <.0001 | .3529  |
| Hispanic                       | 5.4               | 5.9             | 5.2    | 5.3    |
| Missing                        | 3.0               | 5.1             | 3.7    | 3.3    |
| Inpatient, %                   | 91.3              | 90.5            | .0003  | .0003  |
| Fiscal year 2003–2008, %       | 34.1              | 60.8            | <.0001 | .0006  |
| Prior hospitalization, %       | 49.0              | 0.8             | <.0001 | .3648  |
| Comorbidities, %               |                   |                 |        |        |
| Hypertension                   | 775               | 49.8            | <.0001 | 68.2   |
| Dyslipidemia                   | 54.7              | 37.7            | <.0001 | 48.2   |
| Obesity                        | 16.4              | 12.3            | <.0001 | 14.6   |
| Myocardial infarction          | 11.1              | 2.1             | <.0001 | 5.5    |
| CHF                            | 26.1              | 5.6             | <.0001 | 13.7   |
| PVD                            | 18.8              | 6.7             | <.0001 | 12.6   |
| CVD                            | 19.2              | 7.2             | <.0001 | 13.5   |
| Dementia                       | 3.8               | 1.1             | <.0001 | 2.6    |
| COPD                           | 37.7              | 16.3            | <.0001 | 29.2   |
| Rheumatologic disease          | 2.7               | 1.2             | <.0001 | 2.2    |
| Peptic ulcer disease           | 4.6               | 1.2             | <.0001 | 2.8    |
| Liver disease                  | 70                | 1.3             | <.0001 | 4.0    |
| Diabetes                       | 40.3              | 23.4            | <.0001 | 32.6   |
| Hemiplegia/paraplegia          | 3.8               | 0.7             | <.0001 | 2.2    |
| Renal disease                  | 27.7              | 4.9             | <.0001 | 13.1   |
| Cancer                         | 26.6              | 12.6            | <.0001 | 20.2   |
| HIV/AIDS                       | 1.8               | 0.7             | <.0001 | 1.4    |
| GERD                           | 26.7              | 14.1            | <.0001 | 21.7   |
| Transplant                     | 1.9               | <0.1            | <.0001 | <0.1   |
| IBD                            | 2.2               | 0.6             | <.0001 | 1.6    |
| IBS                            | 1.1               | 0.6             | <.0001 | 0.9    |
| Medications, %                 |                   |                 |        | 1.0000 |
| Prior antibiotics              | 55.4              | 16.5            | <.0001 | 27.4   |
| Prior acid suppressant         | 55.7              | 23.8            | <.0001 | 33.3   |
| Prior opioid analgesic         | 38.0              | 15.1            | <.0001 | 22.0   |
| Prior antidiarrheals           | 7.2               | 1.0             | <.0001 | 2.9    |
| Prior bowel prep               | 15.1              | 2.4             | <.0001 | 5.4    |
| Antidepressant use, %          | 34.8              | 21.4            | <.0001 | 26.2   |
| SSRI                           | 21.4              | 14.0            | <.0001 | 16.6   |
| SNRI                           | 3.2               | 2.2             | <.0001 | 2.6    |
| Bupropion                      | 3.5               | 3.3             | .0394  | 3.1    |
| Trazodone                      | 11.7              | 5.6             | <.0001 | 7.5    |
| Mirtazapine                    | 4.9               | 1.9             | <.0001 | 3.3    |
| Tricyclic antidepressants      | 5.5               | 2.3             | <.0001 | 3.8    |
| 2+ antidepressant classes      | 11.7              | 6.3             | <.0001 | 8.2    |
| GABA medication use, %         | 45.1              | 16.8            | <.0001 | 34.5   |
| Benzodiazipine                 | 30.4              | 10.5            | <.0001 | 22.3   |
| Gabapentin                     | 16.8              | 5.9             | <.0001 | 12.9   |
| Zolpidem                       | 6.8               | 1.9             | <.0001 | 3.9    |
| 2+ GABAergic medications       | 11.3              | 2.5             | <.0001 | 7.0    |
| GABAergic + antidepressant     | 21.9              | 8.5             | <.0001 | 14.7   |

Abbreviations: CDI, Clostridioides difficile infection; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; GABA, gamma-aminobutyric acid; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IQR, interquartile range; PVD, peripheral vascular disease; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor.
variables tested. CDI patients were older, had more prior hospitalizations, and had a higher proportion of cardiovascular, metabolic, and inflammatory diseases. Patients with CDI were also significantly more likely to have prior medication use compared with the controls. Following propensity score matching, a total of 18,575 patients remained, including 9,287 patients in each group. Demographics, comorbidities, and prior medications were similar between groups following matching.

In bivariable regression models, antidepressant use overall was not significantly associated with increased risk of CDI (odds ratio [OR], 1.05; 95% CI, 0.98–1.12), although mirtazapine (OR, 1.37; 95% CI, 1.15–1.63) and tricyclic antidepressants (OR, 1.26; 95% CI, 1.08–1.49) were significantly associated with CDI risk (Table 2). In the multivariable model, mirtazapine was positively associated with CDI risk (OR, 1.59; 95% CI, 1.02–2.49), while SSRIs (OR, 0.88; 95% CI, 0.81–0.95) and bupropion (OR, 0.67; 95% CI, 0.57–0.78) were negatively associated with CDI risk throughout the study period (2003 to 2014). These findings varied somewhat by fiscal year of study (2003 to 2008 vs 2009 to 2014) (Table 2).

In bivariable models, GABA medication use was significantly associated with increased CDI risk (OR, 1.81; 95% CI, 1.70–1.92) and even higher risk for those patients with 2 or more recent GABAergic medications (OR, 1.94; 95% CI, 1.70–2.22). Conversely, having both recent GABAergic and antidepressant medication use resulted in lower but significantly elevated CDI risk (OR, 1.43; 95% CI, 1.31–1.56) compared with GABAergic medication alone. In the multivariable model, benzodiazepines were associated with the highest CDI risk (OR, 1.91; 95% CI, 1.77–2.07), followed by gabapentin (OR, 1.45; 95% CI, 1.32–1.60) and zolpidem (OR, 1.23; 95% CI, 1.04–1.45). These trends were relatively consistent by fiscal year of study (Table 2).

In the multivariable model conducted using the entire unmatched cohorts, antidepressant use was not independently associated with CDI risk (OR, 0.95; 95% CI, 0.90–1.00), but GABA medication use was associated with significantly higher CDI risk (OR, 1.95; 95% CI, 1.86–2.06), similar to what was found in the propensity score–matched analyses.

**DISCUSSION**

In this case–control study, we found that recent GABAergic medication use increased risk for CDI among veteran patients, while antidepressant medications did not. To our knowledge, this is the first study to date that has evaluated the association between CDI risk and both antidepressant and GABAergic medication use. Our study is strengthened by its multicenter, nationally representative design with comprehensive data collection and robust statistical control for potential confounders.

While there have been virtually no studies evaluating both medication classes together, previous studies of each medication class have produced similar results. One case–control study by Rogers et al. [19] evaluated the association between antidepressants and development of CDI. A significant association was found with mirtazapine (OR, 2.14; 95% CI, 1.30–3.52; P = .003) and fluoxetine (OR, 1.92; 95% CI, 1.16–3.17; P = .012) and the development of CDI. The study also showed that patients taking both mirtazapine and trazodone had a greater risk of CDI development (OR, 5.72; 95% CI, 2.01–16.26; P = .001) than patients taking either antidepressant alone. In their case–crossover study, trazodone alone (OR, 0.55; 95% CI, 0.33–0.90; P = .018) was negatively associated with CDI risk, while mirtazapine and trazodone combined (OR, 3.25; 95% CI, 2.29–4.62; P = .010) were positively associated with CDI risk, which is consistent with the findings of our study.

**Table 2.** Bivariable and Multivariable Analysis for CDI Risk in the Propensity Score–Matched Cohort (n = 18,574)

| Characteristic                  | Bivariable Regression, OR (95% CI) | 2003 to 2014 (n = 18,574) | 2003 to 2008 (n = 7,525) | 2009 to 2014 (n = 11,049) | Multivariable Regression, OR (95% CI) |
|--------------------------------|-----------------------------------|--------------------------|--------------------------|--------------------------|-----------------------------------|
| Antidepressant use             | 1.05 (0.98–1.12)                  |                          |                          |                          | 0.88 (0.81–0.95)                  |
| SSRI                           | 1.02 (0.95–1.11)                  | 0.88 (0.81–0.95)         | 0.91 (0.80–1.03)         | 0.84 (0.75–0.94)          |
| SNRI                           | 1.13 (0.94–1.26)                  | 0.94 (0.77–1.13)         | 1.09 (0.77–1.55)         | 0.87 (0.70–1.10)          |
| Bupropion                      | 0.77 (0.66–0.91)                  | 0.67 (0.57–0.78)         | 0.67 (0.50–0.88)         | 0.67 (0.55–0.82)          |
| Trazodone                      | 1.06 (0.95–1.19)                  | 0.98 (0.87–1.10)         | 0.75 (0.62–0.90)         | 1.19 (1.02–1.38)          |
| Tricyclic antidepressants      | 1.26 (1.08–1.49)                  | 0.75 (0.50–1.13)         | 0.47 (0.26–0.83)         | 1.30 (0.71–2.40)          |
| Mirtazapine                    | 1.37 (1.15–1.63)                  | 1.59 (1.02–2.49)         | 2.60 (1.35–4.99)         | 0.94 (0.49–1.78)          |
| 2+ antidepressants             | 1.06 (0.96–1.18)                  | —                        | —                       | —                       |
| GABA medication use            | 1.81 (1.70–1.92)                  | —                        | —                       | —                       |
| Benzodiazepine                 | 1.90 (1.75–2.05)                  | 1.91 (1.77–2.07)         | 1.72 (1.53–1.95)         | 2.07 (1.86–2.31)          |
| Gabapentin                     | 1.50 (1.37–1.65)                  | 1.45 (1.32–1.60)         | 1.39 (1.18–1.64)         | 1.50 (1.33–1.69)          |
| Zolpidem                       | 1.37 (1.17–1.61)                  | 1.23 (1.04–1.45)         | 1.18 (0.79–1.76)         | 1.28 (1.07–1.54)          |
| 2+ GABAergic medication        | 1.94 (1.70–2.22)                  | —                        | —                       | —                       |
| GABAergic + antidepressant     | 1.43 (1.31–1.56)                  | —                        | —                       | —                       |

Abbreviations: CDI, Clostridioides difficile infection; GABA, gamma-aminobutyric acid; OR, odds ratio; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor.
Interestingly, we found a negative association between some antidepressants and CDI risk. This negative association between SSRI use and risk of CDI development could be potentially explained by the antimicrobial effects of SSRIs [20]. Previous studies have shown that some SSRIs, namely sertraline, fluoxetine, and paroxetine, have activity against gram-positive bacteria, including *Staphylococcus*, *Enterococcus*, and *Clostridium* species, such as *Clostridium perfringens* and *Clostridium difficile* [20, 21]. Although the mechanisms of how SSRIs may target these bacteria are not completely understood, it is believed that they do so through the inhibition of efflux pumps [22]. Lastly, our study also showed that SNRIs and bupropion had a negative association with CDI risk. Studies have shown that the neurotransmitter norepinephrine can influence growth of other microbes [23, 24], which could potentially influence CDI proliferation and further infection. However, further studies are needed to confirm this association.

With regard to GABAergic medication use, our study found positive associations between CDI and overall GABAergic medication use, as well as individual medication classes. In a retrospective case–control study [25], Ström et al. found that GABAergic medication use overall did not have a significant association with CDI. However, their study did show an increased risk with zolpidem use (OR, 2.89; 95% CI, 1.27–6.60; \( P = .012 \)). This association has also been seen in another case–control study by Dann et al. [10]. This study found that zolpidem use was associated with the development of CDI (OR, 4.88; 95% CI, 1.25–18.34; \( P < .05 \)) in high-risk patients. The relationship between zolpidem and CDI risk is not well understood; however, zolpidem is a selective GABA\(_A\) receptor modulator, which, when activated in other infections like pneumonia, has been shown to impair innate immune function, which results in high bacterial burden and, subsequently, increased mortality [10, 26, 27]. Lastly, while our study indicates increased CDI risk with benzodiazepine and gabapentin use, 1 previous study found nonsignificant associations [25].

This study has potential limitations. First, this study used a retrospective design and data from electronic medical records, which can lead to misclassification bias and confounding. To this end, we supplemented CDI diagnosis codes with a positive stool test and CDI active therapy and used robust multivariable modeling with clinically important confounders. Despite this, we could not control for other potentially important confounders, such as severity of underlying diseases, medication dosage and adherence, site of prescribing (inpatient vs outpatient), and provider treatment decisions (ie, confounding by indication). In addition, propensity score matching has limitations. For example, the reduction of the cohort size due to matching may decrease the generalizability of this study; however, this technique improves the internal validity of the findings. Another potential limitation includes the variability of the CDI diagnostic testing methods used within this study period. Although PCR has been shown to be more sensitive and commonly used compared with toxin enzyme immunoassays, it was not clinically available until 2010 [28]. In addition, with the development of newer tests, the lack of data and clinical availability may have delayed the acceptability of CDI testing during the study period [29]. While we did not directly control for CDI testing given that only the CDI group would have this variable recorded, we matched patients by fiscal year. Additionally, inclusion of all CDI diagnostic measures may improve the generalizability of this study. Finally, this study contained a predominately male veteran population; therefore, study findings might not be generalizable to non–veteran care settings.

**CONCLUSIONS**

In this national cohort of veterans, GABAergic medication use was associated with increased CDI risk, while antidepressant medications were not significant predictors of CDI. Further research is needed to understand the biological mechanisms to support these findings, and confirmatory studies are needed to validate these findings in well-designed prospective human studies.

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**Availability of data.** Data not publicly available.

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