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MAJOR ARTICLE

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 9287 CDI and 9287 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

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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, trazodone, 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 "RxOutpat" 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

	Unmatched Cohorts			Matched Cohorts		
Characteristic	CDI Group (n = 26 149)	Control Group (n = 59 682)	*P* Value	CDI Group (n = 9287)	Control Group (n = 9287)	*P* Value
Age, median (IQR), y	67 (60–78)	61 (52–72)	<.0001	66 (58–77)	66 (59–77)	.4448
Male sex, %	95.9	94.3	<.0001	95.1	95.8	.0188
Race, %			<.0001			.5159
White	70.2	66.8		71.6	72.2	
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	94.1	95.3	.0003
Fiscal year 2003–2008, %	34.1	60.8	<.0001	41.7	39.3	.0006
Prior hospitalization, %	49.0	0.8	<.0001	4.2	4.4	.3648
Comorbidities, %						
Hypertension	77.5	49.8	<.0001	68.2	69.0	.2358
Dyslipidemia	54.7	37.7	<.0001	48.2	47.9	.7135
Obesity	16.4	12.3	<.0001	14.6	14.6	.9834
Myocardial infarction	11.1	2.1	<.0001	5.5	5.1	.2391
CHF	26.1	5.6	<.0001	13.7	14.0	.5661
PVD	18.8	6.7	<.0001	12.6	13.2	.2115
CVD	19.2	7.2	<.0001	13.5	13.7	.7158
Dementia	3.8	1.1	<.0001	2.6	2.5	.7444
COPD	37.7	16.3	<.0001	29.2	28.8	.5825
Rheumatologic disease	2.7	1.2	<.0001	2.2	2.2	.9197
Peptic ulcer disease	4.6	1.2	<.0001	2.8	2.7	.8225
Liver disease	7.0	1.3	<.0001	4.0	4.0	.8807
Diabetes	40.3	23.4	<.0001	32.6	32.9	.6503
Hemiplegia/paraplegia	3.8	0.7	<.0001	2.2	2.2	.8805
Renal disease	27.7	4.9	<.0001	13.1	14.4	.0100
Cancer	26.6	12.6	<.0001	20.2	20.8	.2920
HIV/AIDS	1.8	0.7	<.0001	1.4	1.5	.6199
GERD	26.7	14.1	<.0001	21.7	21.0	.2521
Transplant	1.9	<0.1	<.0001	<0.1	<0.1	.5599
IBD	2.2	0.6	<.0001	1.6	1.5	.8116
IBS	1.1	0.6	<.0001	0.9	0.9	1.0000
Medications, %						
Prior antibiotics	55.4	16.5	<.0001	27.4	28.0	.4032
Prior acid suppressant	55.7	23.8	<.0001	33.3	33.6	.6298
Prior opioid analgesic	38.0	15.1	<.0001	22.0	21.4	.2936
Prior antidiarrheals	7.2	1.0	<.0001	2.9	2.9	.7929
Prior bowel prep	15.1	2.4	<.0001	5.4	5.4	.9222
Antidepressant use, %	34.8	21.4	<.0001	26.2	25.4	.1851
SSRI	21.4	14.0	<.0001	16.6	16.2	.5260
SNRI	3.2	2.2	<.0001	2.6	2.3	.1879
Bupropion	3.5	3.3	.0394	3.1	3.9	.0015
Trazodone	11.7	5.6	<.0001	7.5	7.1	.2711
Mirtazapine	4.9	1.9	<.0001	3.3	2.4	.0004
Tricyclic antidepressants	5.5	2.3	<.0001	3.8	3.0	.0035
2+ antidepressant classes	11.7	6.3	<.0001	8.2	7.7	.2545
GABA medication use, %	45.1	16.8	<.0001	34.5	22.6	<.0001
Benzodiazepine	30.4	10.5	<.0001	22.3	3.7	<.0001
Gabapentin	16.8	5.9	<.0001	12.9	9.0	<.0001
Zolpidem	6.8	1.9	<.0001	3.9	2.8	.0001
2+ GABAergic medications	11.3	2.5	<.0001	7.0	3.7	<.0001
GABAergic + antidepressant	21.9	8.5	<.0001	14.7	10.7	<.0001

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 9287 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, 32.54; 95% CI, 2.29–462.9; $P = .010$) 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)

		2003 to 2014 (n = 18 574)	2003 to 2008 (n = 7525)	2009 to 2014 (n = 11 049)
Characteristic	Bivariable Regression, OR (95% CI)	Multivariable Regression, OR (95% CI)		
Antidepressant use	1.05 (0.98–1.12)			
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.

References

1. Guh AY, Mu Y, Winston LG, et al; Emerging Infections Program *Clostridioides difficile* Infection Working Group. Trends in U.S. burden of *Clostridioides difficile* infection and outcomes. N Engl J Med **2020**; 382:1320–30.
2. Lessa FC, Winston LG, McDonald LC; Emerging Infections Program *C. difficile* Surveillance Team. Burden of *Clostridium difficile* infection in the United States. N Engl J Med **2015**; 372:2369–70.
3. Rao K, Safdar N. Fecal microbiota transplantation for the treatment of *Clostridium difficile* infection. J Hosp Med **2016**; 11:56–61.
4. McFarland LV, Surawicz CM, Stamm WE. Risk factors for *Clostridium difficile* carriage and *C. difficile*-associated diarrhea in a cohort of hospitalized patients. J Infect Dis **1990**; 162:678–84.

5. Bignardi GE. Risk factors for *Clostridium difficile* infection. J Hosp Infect **1998**; 40:1–15.
6. Carabotti M, Scirocco A, Maselli MA, Severi C. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. Ann Gastroenterol **2015**; 28:203–9.
7. Mazzoli R, Pessione E. The neuro-endocrinological role of microbial glutamate and GABA signaling. Front Microbiol **2016**; 7:1934.
8. Krantis A. GABA in the mammalian enteric nervous system. News Physiol Sci **2000**; 15:284–90.
9. Bhat R, Axtell R, Mitra A, et al. Inhibitory role for GABA in autoimmune inflammation. Proc Natl Acad Sci U S A **2010**; 107:2580–5.
10. Dann S, Aitken S, Ross C, et al. Zolpidem confers disease susceptibility to *Clostridium difficile* infection. Gastroenterology **2015**; 4:S727.
11. Reveles KR, Dotson KM, Gonzales-Luna A, et al. *Clostridioides* (formerly *Clostridium*) *difficile* infection during hospitalization increases the likelihood of nonhome patient discharge. Clin Infect Dis **2019**; 68: 1887–93.
12. Bauer MP, Notermans DW, van Benthem BH, et al; ECDIS Study Group. *Clostridium difficile* infection in Europe: a hospital-based survey. Lancet **2011**; 377:63–73.
13. Barbut F, Corthier G, Charpak Y, et al. Prevalence and pathogenicity of *Clostridium difficile* in hospitalized patients. A French multicenter study. Arch Intern Med **1996**; 156:1449–54.
14. Bilgrami S, Feingold JM, Dorsky D, et al. Incidence and outcome of *Clostridium difficile* infection following autologous peripheral blood stem cell transplantation. Bone Marrow Transplant **1999**; 23:1039–42.
15. Bartlett JG. The case for vancomycin as the preferred drug for treatment of *Clostridium difficile* infection. Clin Infect Dis **2008**; 46:1489–92.
16. Gerding DN, Olson MM, Peterson LR, et al. *Clostridium difficile*-associated diarrhea and colitis in adults. A prospective case-controlled epidemiologic study. Arch Intern Med **1986**; 146:95–100.
17. Lin KF, Wu HF, Huang WC, et al. Propensity score analysis of lung cancer risk in a population with high prevalence of non-smoking related lung cancer. BMC Pulm Med **2017**; 17:120.
18. Kim YG, Jang BI, Kim DH, et al. A matched case-control study using the propensity score on differences in the characteristics of colorectal polyps between younger and older Koreans: proximal shift in the distribution of colorectal polyps among older Koreans. Gut Liver **2010**; 4:481–7.
19. Rogers MA, Greene MT, Young VB, et al. Depression, antidepressant medications, and risk of *Clostridium difficile* infection. BMC Med **2013**; 11:121.
20. Munoz-Bellido JL, Munoz-Criado S, Garcìa-Rodrìguez JA. Antimicrobial activity of psychotropic drugs: selective serotonin reuptake inhibitors. Int J Antimicrob Agents **2000**; 14:177–80.
21. Kruszewska H, Zareba T, Tyski S. Examination of antimicrobial activity of selected non-antibiotic medicinal preparations. Acta Pol Pharm **2012**; 69:1368–71.
22. Bohnert JA, Szymaniak-Vits M, Schuster S, Kern WV. Efflux inhibition by selective serotonin reuptake inhibitors in *Escherichia coli*. J Antimicrob Chemother **2011**; 66:2057–60.
23. Biaggini K, Barbey C, Borrel V, et al. The pathogenic potential of *Pseudomonas fluorescens* MFN1032 on enterocytes can be modulated by serotonin, substance P and epinephrine. Arch Microbiol **2015**; 197:983–90.
24. Halang P, Toulouse C, Geißel B, et al. Response of *Vibrio cholerae* to the catecholamine hormones epinephrine and norepinephrine. J Bacteriol **2015**; 197:3769–78.
25. Ström J, Tham J, Månsson F, et al. The association between GABA-modulators and *Clostridium difficile* infection - a matched retrospective case-control study. PLoS One **2017**; 12:e0169386.
26. Huang CY, Chou FH, Huang YS, et al. The association between zolpidem and infection in patients with sleep disturbance. J Psychiatr Res **2014**; 54:116–20.
27. Torres SR, Fröde TS, Nardi GM, et al. Anti-inflammatory effects of peripheral benzodiazepine receptor ligands in two mouse models of inflammation. Eur J Pharmacol **2000**; 408:199–211.
28. Gerding DN, File TM Jr, McDonald LC. Diagnosis and treatment of *Clostridium difficile* infection (CDI). Infect Dis Clin Pract (Baltim Md) **2016**; 24:3–10.
29. Cohen SH, Gerding DN, Johnson S, et al; Society for Healthcare Epidemiology of America; Infectious Diseases Society of America. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). Infect Control Hosp Epidemiol **2010**; 31:431–55.