TITLE: Depression, antidepressant medications and risk of *Clostridium difficile* infection

RUNNING TITLE: Depression and *Clostridium difficile* infection

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ABSTRACT:

Background: An ancillary finding in previous research suggested that the use of antidepressant medications increased the risk of developing *Clostridium difficile* infection (CDI). Our objective was to evaluate whether depression or the use of antidepressants altered the risk of developing CDI using two distinct datasets and study designs.

Methods: In Study 1, we conducted a longitudinal investigation of a nationally-representative sample of older Americans (n=16,781), linking data from biennial interviews to physician visits, hospital stays, emergency department visits, skilled nursing facility stays, home health visits and other outpatient visits. In Study 2, we completed a clinical study of hospitalized adults who were tested for *C. difficile* (n=4047), with cases testing positive and controls testing negative. Antidepressant medication use prior to testing was extracted.

Results: The population-based rate of CDI in older Americans was 282.9/100,000 person-years (95% CI: 226.3, 339.5) for individuals with depression and 197.1/100,000 person-years for those without depression (95% CI: 168.0, 226.1). The odds of CDI were 36% greater in persons with major depression (95% CI: 1.06, 1.74), 35% greater in individuals with depressive disorders (95% CI: 1.05, 1.73), 54% greater in those who were widowed (95% CI: 1.21, 1.95), and 25% less in adults who did not live alone (95% CI: 0.62, 0.92). Self-report of feeling sad or having emotional, nervous or psychiatric problems at baseline were also associated with the later development of CDI. Use of certain antidepressant medications during hospitalization was associated with altered risk of CDI.

Conclusions: Adults with depression and who take specific antidepressants appear to be more likely to develop CDI. Older adults who are widowed or who live alone are also at greater risk of CDI.

BACKGROUND

Clostridium difficile infection (CDI) is the most commonly diagnosed cause of antibiotic-associated diarrhea and has emerged as a major nosocomial infection, surpassing methicillin-resistant *Staphylococcus aureus* in some hospitals.[1] In addition to causing more than 7,000 deaths annually in the United States,[2] it is prevalent in hospitals throughout Europe with a mean frequency of 23 cases for every 10,000 admissions.[3] Concerted efforts to identify modifiable risk factors for CDI are motivated by the significant need for better preventive and therapeutic options against this infection.

Modifiable risk factors of CDI include several classes of medications such as proton pump inhibitors and histamine-2 receptor antagonists.[4] Antidepressants have also been implicated.[5] In a cohort study of 14,719 hospitalized patients, an ancillary finding of an association between antidepressant medications and CDI was reported, which was stronger than that found for proton pump inhibitors or histamine-2 receptor antagonists.[5] A possible link between antidepressant medications and CDI is noteworthy since, worldwide, depression is the third most prevalent disabling condition, as reported by the World Health Organization.[6] Effects of depression have been shown to include alterations in the gut microbiota and increased intestinal permeability.[7-9] In the murine model, behavioral depression increases jejunal permeability and susceptibility to colitis.[10] In population-based human studies, depression was found to be significantly predictive of inflammatory bowel disease.[11,12]

Since the publication of the Dalton et al. study linking antidepressant use with the risk of CDI,[5] there has been no evidence, to our knowledge, to support or refute this finding. Therefore, we

planned an investigation to assess whether depression or the use of antidepressants alters the risk of CDI. We tested these hypotheses using two distinct but complementary approaches. First, we assembled longitudinal data from a nationally-representative sample of older Americans so that these relationships could be assessed in a more generalizable population. Second, we utilized a clinical database of adults admitted to an academic hospital so that details regarding antidepressant use would be available.

METHODS

Study 1

We conducted a longitudinal study to determine population rates of CDI in individuals with and without depression and to evaluate the association between depression and CDI. Subjects were participants in the nationally-representative Health and Retirement Study (HRS) which is an ongoing longitudinal study of older Americans. Details regarding the study design of the HRS and subject characteristics have been published.[13] Households were selected using multistage area probability sampling from the National Sample frame, with random selection of eligible individuals within the household. Subjects were interviewed every two years, from 1992 to the present. Data from the interviews were linked to files from the Centers for Medicare and Medicaid Services (CMS), years 1991-2007, for fee-for-service beneficiaries. The CMS Standard Analytical Files used were the Inpatient, Outpatient, Skilled Nursing Facility, Carrier (Part B), Home Health Agency, and Denominator files.

CDI was determined from a physician's diagnosis of *C. difficile* infection (ICD-9-CM code 008·45) recorded in Inpatient, Outpatient, Carrier, Skilled Nursing Facility or Home Health

Agency files. This captured both outpatient and inpatient diagnoses of CDI. The positive and negative predictive values of the ICD-9-CM code for identifying CDI have been previously reported as 87% and 96%, respectively.[14] Depression was determined from a physician's diagnosis of major depression (ICD-9-CM codes 296.2x, 296.3x, 300.4, 311) at any time prior to a diagnosis of CDI. We also captured a wider group of patients with "depressive disorders" which included brief or prolonged depressive reactions, adjustment reaction with anxiety and depression, depressive type psychosis, chronic depressive personality disorder, bipolar affective disorder with depression, neurotic depression, depressive disorder (not elsewhere classified), as well as major depression (ICD-9-CM codes 296.2x, 296.3x, 296.5, 298.0, 300.4, 301.12, 309.0, 309.1, 309.28, 311, V79.0) diagnosed at any time prior to the diagnosis of CDI. A visit to a psychiatrist was determined from the Carrier (individual provider) file using Berenson-Eggers Type of Service (BETOS) code M5B (evaluation and management by a specialist – psychiatry). Other items related to depression were determined from the initial interview of the HRS. The questions were, "During the past week, did you feel sad?" and "Did a doctor ever tell you that you had emotional, nervous or psychiatric problems?" We also assessed marital status at the time of the first interview (married or partnered, divorced or separated, single, widowed). Since household information was available, we extracted data regarding the number of people in the household at the time of the first interview.

Information was also extracted from the HRS regarding year of birth, gender, race, ethnicity, region of residence (Northeast, Midwest, South, West), body mass index (kg/m^2) at the time of the first interview, smoking status at the time of the first interview (never, former, current), end-stage renal disease at the time of the first interview, and diagnoses of Crohn's disease, irritable

bowel syndrome, ulcerative colitis, or celiac disease (prior to the first CDI diagnosis for those with CDI). We anticipated that some individuals would have greater contact with physicians and medical services and, therefore, we also calculated the number of infection-related visits (inpatient and outpatient) and the total number of medical-related visits (inpatient and outpatient) over the entire period of observation for each subject. Number of infection-related visits was the crude proxy for exposure to antibiotics. Missing values were imputed for the variables race (n=37), ethnicity (n=3), region of residence (n=28), body mass index (n=30) and smoking status (n=91). Calendar year of the first interview was also included to account for secular trends.

Survey-weighted population-based rates of CDI (number of individuals with the diagnosis of CDI per 100,000 person-years of observation) were calculated for individuals with and without major depression. The rates were stratified by subject characteristics (age, gender, race, ethnicity, body mass index, education and region of residence). Survey-weighted logistic regression (svy: logistic) was used to assess the association between depression and CDI, offset by the natural log of the person-years under observation, after adjustment for year of birth (centered), gender, race, ethnicity, body mass index, smoking, end-stage renal disease, Crohn's disease, celiac disease, ulcerative colitis, irritable bowel disease, number of infection-related visits, and total number of medical-related visits. Alpha was set at 0.05, 2-tailed.

Study 2

A hospital-based case-control study was conducted to evaluate the association between antidepressant medications and hospital-acquired CDI. Subjects were all adult patients (18 years or older) hospitalized in the University of Michigan Health System (UMHS) from August 2010

through February 2012 who had their stools tested for *C. difficile*. Stool was tested for *C. difficile* by the UMHS Clinical Microbiology Laboratory. Testing was performed on stools using the C. DIFF QUIK CHEK COMPLETE® test for glutamate dehydrogenase (GDH) antigen and toxins A or B (Techlab, Inc., Blacksburg, VA). All antigen/toxin discordant stool tests were subjected to analysis for the tcdB gene by real-time PCR (BD GeneOhm™ Cdiff Assay; Franklin Lakes, New Jersey). Since hospital-acquired infection was of interest, patients admitted for reason of *C. difficile* (principal diagnosis of CDI) were excluded. Cases were patients who tested positive for CDI ≥48 hours after admission and controls were patients who tested negative for CDI ≥48 hours after admission. Since CDI testing is usually ordered for symptomatic patients (e.g., antibiotic-associated diarrhea), cases and controls were suspected *a priori* to be fairly concordant on these general characteristics. For individuals with multiple *C. difficile* tests, the first test was used for purposes of this study. Data regarding patient demographics, comorbidities and medications (prior to the date of stool collection for CDI testing) were extracted from the electronic hospital data system. Detailed information was available regarding the dosages and dates in which medications were given to each patient.

To assess differences in patient characteristics by case-control status, Pearson's chi-squared test for categorical data, Student t-test for differences in mean age, and Kruskal-Wallis test for differences in length of stay prior to stool collection were utilized. Unconditional logistic regression was used to assess the association between antidepressant use and CDI with and without adjustment for age, gender, race, antibacterial medications, proton pump inhibitors, histamine-2 receptor antagonists, statins, irritable bowel syndrome, celiac disease, Crohn's disease and ulcerative colitis.

Finally, we conducted a sensitivity analysis for the case-control study using different controls. We conducted a case-crossover study in which each patient served as his/her own control. This was done to evaluate differences in antidepressants while controlling for past history of depression. It incorporates a within-person comparison whereby the use of medications is compared over different time periods for the same patient and therefore, it can be used to separate the effects of the antidepressants from the effects of the disease itself (pathophysiology of depression). Such an approach also controls for factors that are difficult to capture, such as genetic profile and past dietary habits. UMHS hospitalizations in which hospital-acquired CDI occurred (n=406) were compared with subsequent hospitalizations (n=949) for the same patient in which CDI did not occur (July 2009 through June 2012). Odds ratios were calculated using a conditional logit model for panel data (clogit), offset by the natural log of the time at risk for infection (length of stay for hospitalizations without CDI; length of time from admission to stool collection for positive *C. difficile* for hospitalizations with CDI). Statistical analyses were performed by using Stata/MP 11·2 (StataCorp LP, College Station, TX, USA). Alpha was set at 0.05, 2-tailed. The studies received human subjects approval at the University of Michigan. Since retrospective electronic data were utilized for the studies, patient consent was waived.

RESULTS

Study 1

Among the 16,781 participants in the linked HRS-CMS database, the mean age at the time of the first interview was 67.9 years (SD, 10.6) and 56.2% were women (Table 1). At baseline, the majority were either overweight (BMI 25.0-29.9 kg/m^2) or obese (BMI $\geq$30 kg/m^2). Of the

16,781 subjects, there were 404 individuals diagnosed with CDI at least once in their Medicare records. Of the 404 people diagnosed with CDI, 142 (35%) had a diagnosis of major depression and 150 (37%) had a diagnosis of a depressive disorder prior to CDI. The rates of CDI in the reference population (fee-for-service Medicare population in the US) are given in Table 1, stratified by major depression. The rate of CDI was 282.9 per 100,000 person-years in those with depression and 197.1 per 100,000 person-years in those without depression.

After adjusting for demographic characteristics, comorbidities and frequency of medical visits, there was a 36% increased odds of developing CDI in individuals with major depression compared to those without (Table 2). The findings were similar for depressive disorders (OR, 1.35), feeling sad (OR, 1.41) and emotional, nervous or psychiatric problems (OR, 1.47). Older Americans who were widowed were significantly more likely to develop CDI; the odds of CDI were 54% greater in older adults who were widowed compared to those who were married. Being divorced or separated was significantly associated with CDI in the unadjusted model but was not in the fully adjusted model (p=0.072). Developing CDI was also more common in older adults who lived alone. Individuals who lived with others had 25% decreased odds of developing CDI compared to those who lived alone.

Study 2

In Study 2, there were 4047 adult patients who had their stools tested for *C. difficile* while hospitalized within the UMHS from 1 August 2010 through 29 February 2012. Of these subjects, 468 tested positive (cases) and 3579 tested negative (controls). Characteristics of the patients are given in Table 3 and demonstrate that the cases and controls were similar with regard

to age, gender, race, type of admission, number of days from admission to the time of stool collection for testing, and use of various medications prior to the stool collection. As seen in Table 3, 83.8% of the cases and 82.6% of the controls received antibiotics (p=0.530). We also had data regarding both antibiotics and antidepressants. In this study, 82.8% of those receiving antidepressants were given antibiotics and 82.7% of those not receiving antidepressants were given antibiotics (p=0.957).

Certain antidepressants were significantly related to *C. difficile* infection (Table 4). The odds of testing positive for *C. difficile* were twice as great in patients who received mirtazapine than in those who did not (OR, 2.14). For each dose of mirtazapine given, the odds of testing positive for *C. difficile* increased by 8%. There was also an association between fluoxetine and testing positive for *C. difficile,* with an odds ratio of 1.92 after adjustment. For each dose of fluoxetine received, the odds of testing positive increased by 6%. Other selective serotonin reuptake inhibitors, besides fluoxetine, were not significantly associated with a positive CDI test. Of the tricyclic antidepressants, each dose of nortriptyline was associated with an 11% increase in the odds of testing positive for *C. difficile*, although the odds ratio for use (yes/no) was not significant at the 0.05 alpha level (p=0.062). The remaining antidepressants were not associated with a positive *C. difficile* test.

In a secondary analysis, we considered whether interactions between antidepressants could alter the risk of developing CDI. There was a significant interaction between mirtazapine and trazodone (p=0.040 for the interaction term). When a patient received both of these antidepressants, the odds of a positive *C. difficile* test were 5.72 times greater than in individuals

receiving neither of these drugs (95% CI: 2.01, 16.26; p=0.001). Of patients receiving mirtazapine only, 21.2% had a positive *C. difficile* test. Of patients receiving trazodone only, fewer patients (13.6%) had a positive test. Of patients receiving both mirtazapine and trazodone, 43.7% subsequently had a positive *C. difficile* test.

In a sensitivity analysis using a case-crossover design whereby patients (n=406) served as their own controls, the interaction between mirtazapine and trazodone remained significant (p=0.010) after adjustment for antibacterial medications, statins, immunosuppressant medications, red blood cell transfusions, proton pump inhibitors, and histamine-2 receptor antagonists (Table 5). The odds of CDI were greater during hospitalizations in which the patients received mirtazapine with trazodone compared to hospitalizations in which these same patients did not receive these two antidepressants. However, the attributable risk associated with these two drugs was small since there were only 1.25% of the hospitalizations in which patients received both of these antidepressants.

DISCUSSION:

Our findings suggest that depression and/or the use of specific antidepressants are associated with developing CDI. Data from a nationally-representative sample of older Americans demonstrate that population-based rates (which include both community-acquired and hospital-acquired disease) are greater in individuals with major depression and depressive disorders, as well as in people who reported feeling sad, or having emotional, nervous or psychiatric problems, after adjustment for confounders. In addition, widowed persons and those living alone were significantly more likely to develop CDI. Results from our clinical study indicate that there

may be certain antidepressants that impart greater risk of CDI, in particular, the combination of mirtazapine with trazodone. Such effects were independent of antibiotic use.

There is experimental and epidemiologic evidence to support the hypothesis that depression and bereavement result in changes in the gastrointestinal system.[7-10,15-17] In a mouse model, depression (i.e., maternal separation) was shown to result in colitis and a greater severity of colitis.[10] In humans, pyrosequencing analysis of fecal microbiota of depressed patients showed distinct bacterial phylotypes compared to those found in patients without depression.[16] Moreover, patients with depressive symptoms exhibit greater and more prolonged inflammatory responses after antigen challenge than individuals without depressive symptoms, suggesting that depression may result in immune dysregulation.[18] Bereavement has also been shown to decrease neutrophil superoxide production in older adults[19] and to reduce the functional activity of natural killer cells.[20] It is possible that the physiologic sequelae of depression itself, and not antidepressants *per se*, may be associated with CDI risk.

It has been suggested that the mechanisms underlying the brain-gut axis may be bidirectional.[21-23] In a 12-year prospective study, the relationship between anxiety, depression and functional gastrointestinal disorders appeared bidirectional in that psychiatric disorders predicted gastrointestinal disease and vice versa.[21] A population-based longitudinal study in the Netherlands found similar results; the risk of developing severe bowel disease was significantly higher in individuals with previous depression, and the risk of developing depression was significantly higher in individuals who previously had severe bowel disease.[22] The authors concluded that depression and severe non-cancerous bowel disease were "varying expressions of

a partly shared aetiological process."[23] Animal studies have suggested similar effects, with the possibility that this interplay may begin in early life.[23,24] Our studies suggest that depression, widowhood, living alone, and the use of antidepressant medications preceded the onset of CDI. We found, in the nationally representative sample, that 35% of those who developed *C. difficile* infection were diagnosed with major depression prior to the infection. However, we did not have the complete medical history of the subjects prior to the entry into these studies and therefore, cannot be certain whether CDI pre-dated entry into our studies for some of the subjects. It is possible that there is a lifelong liaison between the gut microbiota and neurologic response to external stimuli.

In our population-based Study 1, individuals with major depression had rates of *C. difficile* infection that were consistently elevated across all age groups (Table 1). For people without major depression, the rates of *C. difficile* infection increased with age. Note that the rate of *C. difficile* was 332.9/100,000 person-years in the youngest age group in those with depression. It was 301.0/100,000 person-years in the oldest age group for those without depression. If infection with *C. difficile* is a crude indicator of gut health, it would appear that the microbiota of people with depression would be more similar to that of the very aged. Studies of the microbiota of older adults generally show less diversity – particularly those who live in long-term residential care as compared with community dwellers.[25]

The relationship between depression and inflammatory bowel disease is well known.[11,12,26] A strong association between antidepressants and inflammatory pouch syndrome has also been shown (adjusted odds ratio of 4·17; p=0·0002).[27] Because of this, we adjusted for Crohn's

disease and ulcerative colitis in our studies and the relationship between depression and CDI remained. This may indicate that mechanisms underlying colitis due to CDI and colitis due to inflammatory bowel disease demonstrate commonality, both involving host immune response and gut microbiota; when considered independently, each of these types of colitis is associated with depression.

We cannot completely discern whether it is the pathophysiology of depression itself or the treatment for depression that is the major driver of these findings. In the case-control study, we categorized the antidepressants by mechanism of action but this categorization did not perfectly discriminate between those drugs which were associated with higher CDI risk from those that were not. It is widely appreciated that the mechanisms of action of many antidepressants are complex and all effects (both attributable to intended and side effects) are not fully characterized. Many of the antidepressants work by altering serotonin levels and, in the animal model, Ghia and colleagues found that serotonin plays a key role in the pathogenesis of colitis.[28] Yet, even antidepressants within the same general class may have slightly different actions; for example, fluoxetine has a longer half-life than other selective serotonin reuptake inhibitors and has a greater incidence of weight loss and stimulant effects.[29] It is also possible that inter-patient variation in genes encoding for serotonin receptors may play a role in mediating responses to therapy. For example, in a double-blind randomized controlled trial of older patients taking mirtazapine versus paroxetine, side effects were strongly associated with the HTR2A C/C genotype in those receiving paroxetine but there was no effect with mirtazapine – suggesting that underlying genetic markers can impact the mechanism of action as well.[30] In our investigation, the case-crossover design provided some insights regarding discrimination between effects due

to the pathophysiology of depression *per se* versus those due to specific anti-depressants. In this study, personal history of depression was, by design, held constant because of the within-person comparison and therefore, any difference found in antidepressant use was not due to a history of depression. In effect, we measured drug use at different times (hospitalizations) in the same individual. In these analyses, we found that taking most types of antidepressants did not affect the likelihood of developing *C. difficile* infection. However, in a small group of patients, there was a significantly elevated risk of *C. difficile* infection when taking both mirtazapine and trazodone together. The use of trazodone alone appeared protective but when combined with mirtazapine, the risk was elevated. Larger studies are necessary for confirmation of these findings. However, this only occurred in a minority of patients with *C. difficile* infection which suggests that, for most patients, there are underlying pathophysiologic mechanisms of depression that result in their increased risk of *C. difficile* infection – independent of antidepressant use.

While antibiotic use is closely associated with *C. difficile* infection, it is not evident that the link between depression and *C. difficile* infection is due to increased physician prescriptions for antibiotics in individuals with depression. In Study 2, we had a tightly-matched group of controls to cases with respect to antibiotic use. All subjects were individuals whose stool samples were tested for *C. difficile,* which were ordered when antibiotic-associated diarrhea was evident. We found that 83.8% of the cases and 82.6% of the controls received antibiotics (p=0.530). Furthermore, 82.8% of those receiving antidepressants were given antibiotics and 82.7% of those not receiving antidepressants were given antibiotics (p=0.957). Adjustment for antibiotic use in the regression models (as well as for the number of doses of antibiotics) did not change the results.

Our investigation was limited by its observational design, especially for the assessment of antidepressants, since effects of medication are best addressed through trials. However, CDI is not a common outcome and a trial of such unintended effects may not be feasible. Although the relationship between antidepressants and CDI was first reported in a study conducted in two hospitals,[5] unfortunately the types of antidepressants were not listed and therefore, we cannot adequately assess the similarity of results across hospitals. In Study 1, the use of a nationally-representative sample which captured both outpatient visits and inpatient stays over an extended period of time (17 years maximum) was a strength for the assessment of depression, widowhood and other factors in which randomization is not possible.

A limitation of Study 1 is the use of physician diagnoses to detect depression which may underestimate the true frequency of this disease. However, data from the Health and Retirement Study contains additional information beyond physician diagnoses. Information was available from self-report by participants during biennial interviews. The variables shown in Table 2 relate to depression measured in different ways and the odds ratios all tend to show a similar pattern. For example, the patient's report of feeling sad (irrespective of a physician's diagnosis) was significantly associated with *C. difficile* infection. The odds ratio was 1.41 (p=0.008) which parallels the findings for a physician's diagnosis of major depression (OR=1.36, p=0.016). Moreover, if underestimation of depression is present through missed diagnoses, it is likely to be nondifferential misclassification. That is, the under-reporting of depression could occur in people who have *C. difficile* infection as well as in people who do not have *C. difficile* infection. There is currently no established link between depression and *C. difficile* in the medical literature

whereby physicians across the country would link these two conditions. When such nondifferential misclassification occurs, the odds ratio tends to be pulled towards the null. So, if under-diagnosis of depression does occur, we would expect that the true (reference population) odds ratio would be greater than 1.36.

Another concern may be testing bias. Testing bias would occur if the ordering of a test for *C. difficile* occurs at different rates in persons with and without depression. In Study 2, participants were all patients who were tested for *C. difficile* during a given time period because of symptoms evidenced during hospitalization – that is, antibiotic-associated diarrhea. Since depression has not been previously correlated with *C. difficile* in the medical literature or in general clinical practice, we do not suspect that there was differential testing based on this specific diagnosis.

Unfortunately, questions regarding dietary intake were not asked of all participants in the Health and Retirement Study as a part of the ongoing biennial interviews. Nor do we have dietary intake information on the hospitalized patients in Study 2. Therefore, the influence of habitual diet on both depression and *C. difficile* cannot be assessed in our studies. There was one aspect of our investigation, however, in which we were able to control for past dietary intake. In the sensitivity study of the hospitalized patients (Study 2), we conducted a case-crossover study whereby each person was compared to him/herself. In this instance, past dietary habits (prior to July 2009) were held constant; such habits are the same because the person is the same. When diet was held constant, patients receiving mirtazapine with trazodone were at greater risk of developing CDI. However, if some of these patients began eating differently after July 2009,

such differences could not be measured. Overall, the impact of diet on both depression and *C. difficile* infection would be an interesting area for further study.

CONCLUSIONS:

Given the rise of CDI, especially among older individuals,[31] elucidating the modifiable risk factors for this often-fatal illness is an important patient safety issue. Our complementary studies reveal that adults with depression and those that use specific antidepressants appear more likely to experience CDI. Widowhood and living alone were also associated with CDI. Clinicians prescribing antimicrobials to patients with depression should be aware of the possible increased risk of CDI in this patient population.

LIST OF ABBREVIATIONS:

CDI: *Clostridium difficile* infection

HRS: Health and Retirement Study

CMS: Centers for Medicare and Medicaid Services

UMHS: University of Michigan Health System

CI: Confidence interval

COMPETING INTERESTS:

None.

AUTHORS' CONTRIBUTIONS: MAMR, MTG and DMA participated in designing the studies. MAMR generated the hypotheses. VBY, KML and DMA provided resources. MAMR and MTG extracted the data. MAMR had full access to all of the data, conducted the analyses and wrote the first draft of the report. MAMR, MTG, VBY, SS, KML, JYK and DMA participated in interpretation of the data, writing the manuscript, and critically reviewing the paper. All authors approved the final manuscript.

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TABLE 1. Rate of *Clostridium difficile* Infection by Previous Diagnosis of Major Depression, Medicare Beneficiaries

		No Depression		Depression	
Characteristics	**n (%), sample**	**Rate[a]**	**95% CI**	**Rate[a]**	**95% CI**
Age at first interview[b]					
<60 years	5277 (31.4%)	125.1	82.2, 168.0	332.9	193.5, 472.2
60-75 years	7258 (43.3%)	178.2	145.2, 211.1	239.8	182.9, 296.7
>75 years	4246 (25.3%)	301.0	241.6, 360.3	321.6	213.4, 429.9
Gender					
Men	7352 (43.8%)	179.6	145.5, 213.6	268.9	163.5, 374.3
Women	9429 (56.2%)	212.2	173.6, 250.8	289.3	233.6, 345.1
Race					
African-American	2232 (13.3%)	221.5	136.7, 306.2	346.4	173.6, 519.3
Other	14549 (86.7%)	193.1	161.7, 224.5	275.1	214.5, 335.7
Ethnicity					
Mexican-American	700 (4.2%)	243.7	77.3, 410.1	313.1	65.6, 560.7
Other Hispanic	486 (2.9%)	204.9	272.4, 382.6	234.2	129.8, 338.6
Non-Hispanic	15595 (92.9%)	195.1	165.5, 224.6	283.6	222.3, 344.9
Body mass index					
<18.5 kg/m^2	366 (2.2%)	348.2	87.9, 608.6	475.5	115.3, 835.6
18.5-24.9 kg/m^2	6311 (37.6%)	185.0	149.2, 220.8	279.0	185.7, 372.2
25.0-29.9 kg/m^2	6851 (40.8%)	188.4	151.7, 225.1	300.8	210.7, 390.9
≥30.0 kg/m^2	3253 (19.4%)	225.4	160.6, 290.1	234.9	133.5, 336.3
Education					
No high school degree	5691 (33.9%)	247.6	203.2, 291.9	254.4	170.5, 338.2
High school degree	11090 (66.1%)	172.1	137.7, 206.5	299.6	234.0, 365.3
Region of residence					
Northeast	2958 (17.6%)	265.3	193.1, 337.4	366.5	194.9, 538.1
Midwest	4205 (25.1%)	226.6	155.5, 297.8	307.0	191.5, 422.5
South	6823 (40.7%)	176.5	135.4, 217.7	257.5	185.6, 329.5
West	2795 (16.7%)	136.1	85.4, 186.7	218.8	115.6, 322.0
Overall	16781	197.1	168.0, 226.1	282.9	226.3, 339.5

a. Number of individuals with *C. difficile*/100,000 person-years.
b. Age range, 36 to 103 years.

TABLE 2. Odds Ratios for *Clostridium difficile* Infection and Previous Depression-related Conditions, Medicare Beneficiaries

	Unadjusted			Adjusted for age, gender, race			Fully Adjusted[a]		
Conditions	**OR**	**95% CI**	**p value**	**OR**	**95% CI**	**p value**	**OR**	**95% CI**	**p value**
Depression									
Yes	1.45	1.14, 1.86	0.003	1.41	1.10, 1.82	0.008	1.35	1.06, 1.73	0.017
No	1.00	(reference)		1.00	(reference)		1.00	(reference)	
Depressive disorders									
Yes	1.44	1.13, 1.85	0.004	1.40	1.08, 1.80	0.011	1.34	1.04, 1.72	0.022
No	1.00	(reference)		1.00	(reference)		1.00	(reference)	
"Felt sad"									
Yes	1.62	1.27, 2.06	<0.001	1.48	1.16, 1.90	0.002	1.38	1.08, 1.76	0.011
No	1.00	(reference)		1.00	(reference)		1.00	(reference)	
"Emotional, nervous or psychiatric problems"									
Yes	1.45	1.02, 2.05	0.038	1.55	1.08, 2.21	0.017	1.45	1.01, 2.08	0.046
No	1.00	(reference)		1.00	(reference)		1.00	(reference)	
Psychiatrist visit									
Yes	1.42	1.10, 1.83	0.008	1.35	1.05, 1.72	0.020	1.26	0.95, 1.67	0.106
No	1.00	(reference)		1.00	(reference)		1.00	(reference)	
Marital status									
Widowed	1.84	1.49, 2.28	<0.001	1.59	1.26, 2.02	<0.001	1.51	1.20, 1.92	0.001
Divorced/separated	1.63	1.02, 2.58	0.040	1.66	1.02, 2.70	0.043	1.52	0.95, 2.42	0.078
Single	1.29	0.63, 2.65	0.473	1.27	0.61, 2.63	0.518	1.26	0.60, 2.62	0.537
Married	1.00	(reference)		1.00	(reference)		1.00	(reference)	
Multiple people in household									
Yes	0.67	0.55, 0.81	<0.001	0.71	0.58, 0.88	0.002	0.76	0.62, 0.92	0.007
No	1.00	(reference)		1.00	(reference)		1.00	(reference)	

a. Adjusted for year of birth (centered), gender, race, ethnicity, body mass index, smoking, end-stage renal disease, Crohn disease, celiac disease, ulcerative colitis, irritable bowel disease, number of infection-related visits, and total number of medical-related visits.

TABLE 3. Characteristics of Hospitalized Adults who Tested Positive (Cases) and Negative (Controls) for *Clostridium difficile*

Characteristics	Cases (n=468)	Controls (n=3579)	p value
Age, mean(SD)[a]	57.6 (17.5)	58.8 (16.5)	0.158
Female, n (%)	223 (47.6%)	1723 (48.1%)	0.841
Caucasian, n (%)	387 (82.7%)	2927 (81.8%)	
African-American, n (%)	51 (10.9%)	386 (10.8%)	
Other race / unknown, n (%)	30 (6.4%)	266 (7.4%)	0.727
Elective admission, n (%)	138 (29.5%)	930 (26.0%)	
Urgent admission, n (%)	104 (22.2%)	846 (23.6%)	
Emergent admission, n (%)	226 (48.3%)	1803 (50.4%)	0.268
Days until stool collection, median (IQR)[b]	6 (4, 10)	6 (4, 10)	0.273
Antibiotics, n (%)	392 (83.8%)	2956 (82.6%)	0.530
Immunosuppressants, n (%)	71 (36.4%)	554 (35.0%)	0.692
Proton pump inhibitors, n (%)	268 (57.3%)	2040 (57.0%)	0.913
Histamine-2 receptor antagonists, n (%)	138 (29.5%)	1061 (29.6%)	0.944
Statins, n (%)	130 (27.8%)	927 (25.9%)	0.385
Anxiolytics, n (%)	67 (34.4%)	499 (31.5%)	0.419
Antipsychotics, n (%)	24 (12.3%)	202 (12.7%)	0.860

a. Age range, 18 to 100 years
b. Number of days from admission to stool collection for Clostridium difficile testing, median and interquartile range.

TABLE 4. Odds Ratios for Antidepressant Medications and *Clostridium difficile* Infection, Hospitalized Adults

		Unadjusted			Adjusted[a]		
Medications	Number using medication	**OR**	**95% CI**	**p value**	**OR**	**95% CI**	**p value**
Noradrenergic & Specific Serotonergic Antidepressants:							
Mirtazapine							
Yes (versus no use)	99	2.11	1.29, 3.45	0.003	2.14	1.30, 3.52	0.003
Number doses given		1.08	1.01, 1.16	0.018	1.08	1.01, 1.16	0.020
Selective Serotonin Reuptake Inhibitors:							
Fluoxetine							
Yes (versus no use)	99	1.98	1.20, 3.26	0.008	1.92	1.16, 3.17	0.012
Number doses given		1.06	1.00, 1.12	0.036	1.06	1.00, 1.12	0.046
Escitalopram							
Yes (versus no use)	80	0.97	0.48, 1.95	0.929	0.98	0.48, 1.97	0.945
Number doses given		1.04	0.98, 1.10	0.191	1.04	0.98, 1.09	0.234
Citalopram							
Yes (versus no use)	310	0.90	0.62, 1.32	0.599	0.90	0.62, 1.31	0.569
Number doses given		0.99	0.94, 1.04	0.620	0.98	0.94, 1.04	0.566
Sertraline							
Yes (versus no use)	207	0.90	0.58, 1.42	0.666	0.88	0.56, 1.39	0.583
Number doses given		0.98	0.93, 1.04	0.486	0.98	0.92, 1.04	0.461
Paroxetine							
Yes (versus no use)	78	0.87	0.42, 1.82	0.716	0.86	0.41, 1.80	0.692
Number doses given		0.98	0.88, 1.09	0.693	0.98	0.88, 1.09	0.680
Tricyclic Antidepressants:							
Nortriptyline							
Yes (versus no use)	49	1.98	0.98, 4.00	0.056	1.96	0.97, 3.97	0.062
Number doses given		1.11	1.02, 1.20	0.015	1.11	1.02, 1.20	0.017
Amitriptyline							
Yes (versus no use)	63	1.45	0.73, 2.88	0.284	1.43	0.72, 2.84	0.307
Number doses given		1.04	0.96, 1.14	0.337	1.04	0.96, 1.14	0.343

Serotonin Antagonist & Reuptake Inhibitors:							
Trazodone							
Yes (versus no use)	405	1.23	0.91, 1.66	0.182	1.21	0.90, 1.65	0.211
Number doses given		1.04	0.98, 1.10	0.184	1.04	0.98, 1.10	0.197
Serotonin-Norepinephrine Reuptake Inhibitors:							
Duloxetine							
Yes (versus no use)	82	1.19	0.63, 2.26	0.597	1.15	0.60, 2.19	0.681
Number doses given		1.01	0.94, 1.09	0.690	1.01	0.94, 1.09	0.788
Venlafaxine							
Yes (versus no use)	58	0.72	0.29, 1.81	0.482	0.71	0.28, 1.78	0.464
Number doses given		1.05	0.95, 1.16	0.367	1.05	0.94, 1.16	0.401
Norepinephrine-dopamine Reuptake Inhibitors:							
Bupropion							
Yes (versus no use)	97	1.08	0.59, 2.00	0.801	1.02	0.55, 1.89	0.948
Number doses given		0.95	0.85, 1.06	0.357	0.94	0.85, 1.05	0.306

a. Adjusted for age, gender, race, antibacterial medications, proton pump inhibitors, histamine-2 receptor antagonists, statins, irritable bowel syndrome, celiac disease, Crohn's disease, and ulcerative colitis.

TABLE 5. Odds Ratios for Antidepressant Medications and *Clostridium difficile* Infection, Case-Crossover Study of Hospitalized Adults

Medications	Number hospitalizations[a]	OR[b]	95% CI	p value
Fluoxetine	53	1.74	0.46, 6.65	0.416
Escitalopram	25	0.57	0.12, 2.79	0.491
Citalopram	128	0.41	0.17, 0.99	0.047
Sertraline	105	0.58	0.21, 1.57	0.282
Paroxetine	18	4.71	0.88, 25.33	0.071
Nortriptyline	30	0.22	0.02, 2.13	0.190
Amitriptyline	38	1.20	0.30, 4.79	0.800
Duloxetine	37	0.44	0.10, 1.89	0.267
Venlafaxine	27	5.05	0.58, 44.15	0.143
Bupropion	36	0.48	0.11, 2.05	0.323
Mirtazapine	64	0.82	0.31, 2.13	0.682
Trazodone	171	0.55	0.33, 0.90	0.018
Mirtazapine & Trazodone[c]	17	32.54	2.29, 462.9	0.010

a. Number of hospitalizations in which medication was administered.

b. Adjusted for antibacterial medications, proton pump inhibitors, histamine-2 receptor antagonists, statins, immunosuppressants & RBC transfusion.

c. Reference category: no mirtazapine & no trazodone.