ORIGINAL ARTICLE

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Antidepressant medications are associated with increased risk of hospital-acquired *Clostridioides difficile* infection: a population-based study

Antoine **BOUSTANY**[1], Somtochukwu **ONWUZO**[1], Hadi Khaled Abou **ZEID**[2], Ashraf **ALMOMANI**[1] and Imad **ASAAD**[1]

[1] Department of Internal Medicine, Cleveland Clinic Foundation, Cleveland, Ohio, United States.
[2] Department of Medicine and Medical Sciences, University of Balamand, Koura, Lebanon.

HIGLIGHTS

What is already known:

- The rate and severity of *Clostridioides difficile* infection (CDI) has increased throughout North America, the United Kingdom, and Europe.
- Scattered evidence about the association of CDI with antidepressant medications use exists in the literature so far.

What are the new findings:

- The risk of *Clostridioides difficile* infection is higher in patients who are on mirtazapine, nortriptyline, or trazodone.
- The prevalence rate of *Clostridioides difficile* infection in patients who were using antidepressant medications and the ones who did not, increased with age.

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Corresponding author: Antoine Boustany. E-mail: boustaa@ccf.org

ABSTRACT – Background – During the past decade, *Clostridioides difficile* infection (CDI) has become the most common cause of antibiotic-associated diarrhea. Several risk factors have been implicated. Scattered evidence about the association of CDI with antidepressant medications use exists in the literature so far. Therefore, we aim to investigate whether the risk of developing CDI is increased in hospitalized patients using antidepressant medications. **Methods –** Patients who were hospitalized were included in our cohort. We excluded individuals aged less than 18 years. A multivariate regression analysis was performed to calculate the risk of CDI accounting for potential confounders. **Results –** The risk of CDI in hospitalized patients was increased in individuals diagnosed with inflammatory bowel disease (OR: 4.44; 95%CI: 4.35–4.52), and in patients using clindamycin (OR: 1.55; 95%CI: 1.53–1.57), beta-lactam antibiotics (OR: 1.62; 95%CI: 1.60–1.64), PPI (OR: 3.27; 95%CI: 3.23–3.30), trazodone (OR: 1.31; 95%CI: 1.29–1.33), nortriptyline (OR: 1.25; 95%CI: 1.21–1.28), and mirtazapine (OR: 2.50; 95%CI: 2.46–2.54). After controlling for covariates, the risk of CDI was not increased in patients who were taking fluoxetine (OR: 0.94; 95%CI: 0.92–0.96). **Conclusion –** In contrary to fluoxetine; mirtazapine, nortriptyline, and trazodone were associated with increased risk of CDI in hospitalized patients.

Keywords – Antidepressant medications, *Clostridioides difficile*, *Clostridioides difficile* infection.

INTRODUCTION

Clostridioides difficile was formerly classified within the Clostridiodes genus. Recent investigations have revealed that it belongs to the Peptoclostridium genus. Nevertheless, in order to circumvent confusion in the medical field and reduce associated economic costs, the scientific community reached a consensus to introduce a novel genus that commences with the letter C. Subsequently, *Clostridiodes difficile* has been renamed as *Clostridioides difficile*[1]. During the past decade, *Clostridioides difficile* has become the most common cause of antibiotic-associated diarrhea[2-4]. The rate and severity of *Clostridioides difficile* infection (CDI) has increased throughout North America, the United Kingdom, and Europe. Thus, investigations into factors accounting for its increasing prevalence and adverse outcome has risen[5]. *Clostridioides difficile* is an anaerobic, spore-forming bacillus that produces an enterotoxin (toxin A) and a cytotoxin (toxin B)[4]. Although CDI is mainly localized to the colon manifesting as diarrhea and pseudomembranous colitis, it may progress to toxic megacolon, sepsis, and death[4,6].

Several risk factors have been implicated in CDI including advanced age, co-morbidities, use of antibiotics, proton pump inhibitors (PPIs), histamine-2 receptor antagonist (H2RA), exposure to healthcare settings, obesity, non-steroidal anti-inflammatory drugs (NSAID), vitamin D, and role of host genetics[7]. Scattered evidence about the association of CDI with antidepressant medications use exists in the literature so far[2,5]. Knowing that the use of antidepressant medications increases with age[8] and that its prescription has dramatically increased over past decades[9], studying the side effects and adverse events associated with it is very valuable and clinically relevant. Therefore, we aim to investigate whether the risk of developing hospital-acquired CDI is increased in patients using antidepressant medications.

METHODS

Database

Explorys Inc., Cleveland, OH, USA is a validated multicenter and research platform database of more than 360 hospitals from 26 different healthcare systems across the United States consisting of data accumulated from 1999 to September 2022. It was developed and has been prospectively maintained by IBM Corporation, Watson Health[10] including electronic health record (EHR) from greater than 60 million unique patients and provide a broad regional distribution of the United States representing approximately 15% of the population. It was utilized to construct a retrospective cohort analysis. A Systematized Nomenclature of Medicine-Clinical Terms (SNOMED-CT) hierarchy[11] was used to select diagnoses, findings, and procedures. Prescription drug orders are mapped into SNOMED and RxNorm[12]. Institutional Review Board (IRB) was not required as source data are de-identified. To protect patient confidentiality, Explorys rounds population counts to the nearest 10 and treats all counts between zero and 10 as equivalent. The study was conducted in accordance to the Declaration of Helsinki (as revised in 2013). Access to the database is granted to participating healthcare systems. Use of the Explorys platform has been validated in multiple fields including gastroenterology[13,14].

Patient selection

Patients who were hospitalized were included in our cohort. We excluded individuals aged less than 18 years. A subgroup of patients who were diagnosed with CDI as in-patient was later selected and used in the analysis. The control group was identified as patients who did not have a diagnosis of CDI.

Statistical analysis

Patients who developed CDI were compared to those who did not. The 1-year incidence of CDI was calculated and compared between patients who were on antidepressants versus the ones who were not. The prevalence rate of CDI in patients on antidepressants was calculated among different age groups, and it was compared to the prevalence rate of infection in patients who were not on antidepressant medications. The prevalence rate of the different types of selective serotonin reuptake inhibitor (SSRI) was calculated. Based on the most prevalent SSRI obtained, and on the evidence present in the literature[2,5], we selected the type of SSRI to be further studied in our regression analysis. A univariate regression mo-

del was used to calculate the risk of CDI. A multivariate regression analysis was performed to account for potential confounders including use of antibiotic medications (clindamycin and beta-lactam), use of antidepressant medications (trazodone, nortriptyline, fluoxetine, and mirtazapine), use of proton pump inhibitor, and a diagnosis of inflammatory bowel disease. A two-sided *P* value <0.05 was considered as statistically significant, and all statistical analyses were performed using R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria, 2008).

RESULTS

Descriptive epidemiology

A total of 81,054,370 patients were screened and 55,664,420 were selected after accounting for inclusion and exclusion criteria. The baseline characteristics of our cohort are displayed in TABLE 1. The 1 year incidence of difficile infection in patients who were not on antidepressant medications was 580 per 10 *Clostridioides* 0,000 individuals (0.58%). The 1-year incidence of CDI in patients who were on antidepressant medications was 770 per 100,000 individuals (0.77%). The prevalence rate of CDI in patients who were using antidepressant medications and the ones who did not, increased with age (FIGURE 1). The prevalence rate of the different types of SSRI was calculated. Sertraline (27%), Citalopram (22%), Escitalopram (22%), and fluoxetine (18%) were the most prevalent SSRI in the U.S population (FIGURE 2). Based on the evidence present in the literature[2,5] and on the most prevalent types of SSRI obtained in this study, we selected fluoxetine to be further studied in our regression analysis.

Female gender (65.12%), Caucasian race (77.15%), type 2 diabetes mellitus (21.12%), IBD (6.11%), IBS (11.08%), smoking (10.89%), and alcohol use (1.84%) were more common in patients with a diagnosis of CDI. The use of clindamycin (13.64%), beta-lactam (49.50%), PPI (46.05%), trazodone (9.56%), nortriptyline (2.05%), fluoxetine (5.68%), and mirtazapine (5.10%) was higher patients diagnosed with *Clostridioides difficile* as well.

TABLE 1. Baseline characteristics of patients with *Clostridioides difficile* infection and control.

		CDI (%)	Control (%)
	Total	n=48,720	n=55,615,700
Sex	Male	16,970 (34.83)	25,363,040 (42.00)
	Female	31,730 (65.12)	29,760,300 (53.51)
Race	Caucasian	37,590 (77.15)	27,624,680 (49.67)
	African American	3,950 (8.10)	5,076,330 (9.12)
	Hispanic	250 (0.51)	685,770 (1.23)
	Asian	290 (0.59)	834,450 (1.50)
Comorbidities	Type 2 Diabetes Mellitus	10,290 (21.12)	2,927,530 (5.26)
	IBD	2,980 (6.11)	159,650 (0.28)
	IBS	5,400 (11.08)	572,850 (1.03)
Substance abuse	Smoking	5,310 (10.89)	2,312,760 (4.15)
	Alcohol	900 (1.84)	192,310 (0.34)
Medication use	Clindamycin	6,650 (13.64)	1,212,610 (2.18)
	Beta-lactam	24,120 (49.50)	7,485,600 (13.45)
	PPI	22,440 (46.05)	4,125,750 (7.41)
	Trazodone	4,660 (9.56)	773,480 (1.39)
	Nortriptyline	1,000 (2.05)	132,380 (0.23)
	Fluoxetine	2,770 (5.68)	673,340 (1.21)
	Mirtazapine	2,530 (5.19)	212,190 (0.38)

CDI: *Clostridioides difficile infection*; IBD: inflammatory bowel disease; IBS: irritable bowel syndrome; PPI: proton pump inhibitor.

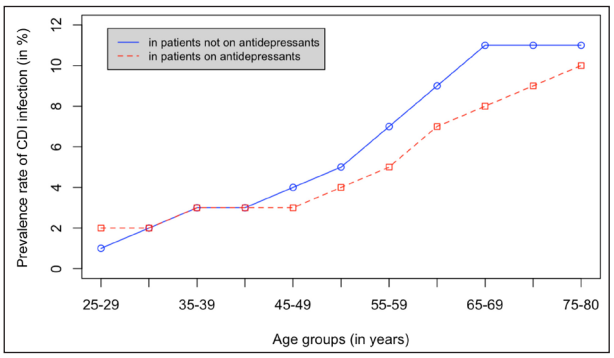

FIGURE 1. Prevalence rate of *Clostridioides difficile* infection among different age groups.
CDI: *Clostridioides difficile* infection.

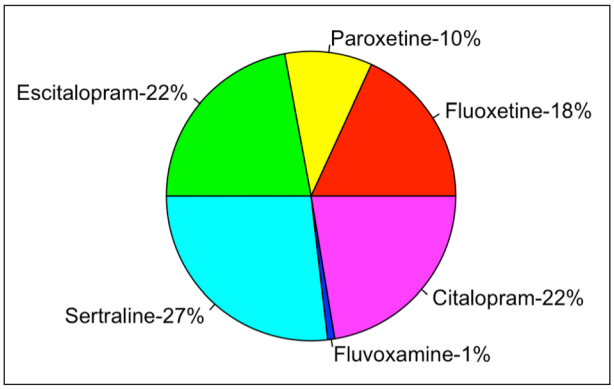

FIGURE 2. Prevalence rate of Selective serotonin reuptake inhibitor (SSRI) subtypes in the U.S adult population.

Risk and predictors of CDI using a univariate regression analysis

The risk of being diagnosed with CDI in hospitalized patients was increased in inflammatory bowel disease (IBD) patients (OR: 7.38; 95%CI: 7.25–7.52). It was also higher in patients using clindamycin (OR: 2.80; 95%CI: 2.77–2.84), beta-lactam antibiotics (OR: 3.21; 95%CI: 3.18–3.24), PPI OR: 4.95; 95%CI: 4.89–4.99), trazodone (OR: 2.70; 95%CI: 2.75–2.82), nortriptyline (OR: 3.02; 95%CI: 2.93–3.11), fluoxetine (OR: 1.90; 95%CI: 1.86–1.94), and mirtazapine (OR: 5.23; 95%CI: 5.15–5.31) (TABLE 2).

Risk and predictors of CDI using a multivariate regression analysis

In order to adjust for confounding variables, a multivariate regression analysis was performed. The risk of CDI in hospitalized patients was increased in individuals diagnosed with IBD (OR: 4.44; 95%CI: 4.35–4.52), and in patients using clindamycin (OR: 1.55; 95%CI: 1.53–1.57), beta-lactam antibiotics (OR: 1.62; 95%CI: 1.60–1.64), PPI (OR: 3.27; 95%CI: 3.23–3.30), trazodone (OR: 1.31; 95%CI: 1.29–1.33), nortriptyline (OR: 1.25; 95%CI: 1.21–1.28), and mirtazapine (OR: 2.50; 95%CI: 2.46–2.54). After controlling for covariates, the risk of CDI was not increased in patients who were using fluoxetine (OR: 0.94; 95%CI: 0.92–0.96) (FIGURE 3).

TABLE 2. Risk of developing *Clostridioides difficile* infection using univariate regression analysis model.

	CDI	
	OR (95%CI)	*P*-value
Clindamycin	2.80 (2.77–2.84)	<0.001
Beta-lactam	3.21 (3.18–3.24)	<0.001
IBD	7.38 (7.25–7.52)	<0.001
PPI	4.94 (4.89–4.99)	<0.001
Trazodone	2.79 (2.75–2.82)	<0.001
Nortriptyline	3.02 (2.93–3.11)	<0.001
Fluoxetine	1.90 (1.86–1.94)	<0.001
Mirtazapine	5.23 (5.15–5.31)	<0.001

CDI: *Clostridioides difficile* infection; CI:confidence interval; IBD: inflammatory bowel disease; OR: odd ratio; PPI: proton pump inhibitor.

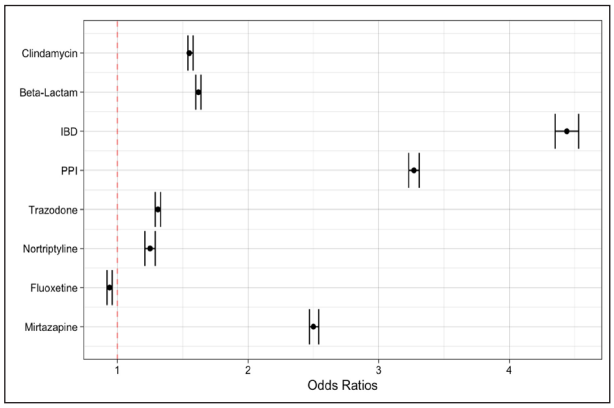

FIGURE 3. Forest plot for risk of developing *Clostridioides difficile* infection.
IBD: inflammatory bowel disease; PPI: proton pump inhibitor.

DISCUSSION

The incidence of CDI has generally been increasing[15]. The first evidence of an association of CDI with antidepressant medications use was described in a cohort study of 14,719 patients[5]. The article aimed to assess the association of proton-pump inhibitors and CDI in a setting of low disease activity. Nine out of 14 drug classes were significantly associated with CDI in a univariate regression analysis. After controlling for confounding variables, only PPI days, histamine-2 receptor antagonists (H2RAs), and anti-

depressants were significantly associated with CDI. However, specific types of antidepressant medication were not investigated. Therefore, another relatively recent study assessing whether major depression or specific types of anti-depressants alter the risk of developing CDI was performed[2]. The risk of CDI was significantly increased in patients with major depression. Using multivariate regression analysis, specific types of antidepressant medications were also associated with a higher risk of CDI including mirtazapine, fluoxetine, nortriptyline, amitriptyline, trazodone, and duloxetine. Results of our study for mirtazapine, nortriptyline, and trazodone are comparable to the ones of Rogers et al.[2]. Regarding fluoxetine, the risk of developing CDI was increased in univariate regression analysis (OR: 1.90; 95%CI: 1.86–1.94). However, after taking into account confounding variables, the risk of CDI was not increased in hospitalized patients who were using fluoxetine compared to the ones who were not using it (OR: 0.94; 95%CI: 0.92–0.96).

The mechanism of action of antidepressant medications is complex and not fully understood[2,16]. It is also unclear how they increase the risk of CDI[2,5,17]. However, it is well known that antidepressants amplify serotonin or norepinephrine signaling by inhibiting reuptake at the synaptic cleft[18]. Alternation of serotonin level could potentially explain the increased risk of CDI[17]. In fact, an experimental study done on mice demonstrated an increased risk of 5-hydroxytryptamine (5-HT) mediated colonic inflammation through activation of immune cells[19]. Jorandli et al. suggested that the reduced serotonin reuptake capacity may contribute to the increased interstitial serotonin level associated with intestinal inflammation[17]. Another hypothesis explaining this unclear mechanism could be the dysregulation of the immune system by antidepressant medications[20]. Abnormalities in the proliferation, cytokine secretion and viability of peripheral blood lymphocytes have been observed in cells exposed to SSRIs. One study evaluating the ex-vivo immunomodulatory effect of SSRI in T cells found that paroxetine and sertraline decreased T-cell viability[21]. Another study illustrated that antidepressants suppressed the production of the Th1 cytokine interferon gamma (IFN-γ)[22].

To the best of our knowledge, this is the largest study to date assessing the risk of CDI with antidepressant medications use in hospitalized patients. We believe that the results of our population-based study reinforce the limited evidence present in the literature. This study has few limitations mainly related to the nature of the database we used. First, the accuracy of the prevalence rates of diagnosis might be affected since the database only includes information of patients who sought medical care. Second, bias in data entry and classification may influence the true estimates of diseases. Despite these limitations, Explorys has been well established previously as a database in different specialties including gastroenterology[13,14]. Third, our study is also limited by the inclusion of hospitalized patients only. Since CDI has emerged in the community in population previously considered low risk[23], analyzing community-acquired CDI would be interesting as well.

CONCLUSION

In conclusion, our study illustrates that the risk of hospital-acquired CDI is higher in patients who are on antidepressant medications compared to the ones who are not. In contrary to fluoxetine; mirtazapine, nortriptyline, and trazodone were associated with an increased risk of CDI in hospitalized patients. The results of this study are in line with those of smaller ones done previously. Future studies will be needed to better understand the mechanism of how antidepressant medications predispose patients to CDI. Considering the rising incidence of CDI in the community, further studies would also be needed to assess to risk of community-acquired CDI with the use of antidepressant medications.

Authors' contribution

Boustany A: first author, study design, methodology and statistics. Onwuzo S, Zeid HKA and Almomani A: manuscript writing. Asaad I: last author, supervision of the study.

Orcid

Antoine Boustany: 0000-0002-4661-1443.
Somtochukwu Onwuzo: 0000-0001-5060-3131.
Hadi Khaled Abou Zeid: 0000-0002-5111-3043.
Ashraf Almomani: 0000-0003-1648-0005.
Imad Asaad: 0000-0002-0648-6625.

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RESUMO – Contexto – Na última década, a infecção por *Clostridioides difficile* (ICD) tornou-se a causa mais comum de diarreia associada a antibióticos. Vários fatores de risco foram implicados. Existem evidências dispersas na literatura sobre a associação da ICD com o uso de medicamentos antidepressivos. Portanto, pretendemos investigar se o risco de desenvolver infecção adquirida na comunidade por *Clostridioides difficile* aumenta em pacientes que usam medicamentos antidepressivos. **Métodos –** Pacientes que foram hospitalizados foram incluídos em nossa coorte. Indivíduos com menos de 18 anos foram excluídos. Uma análise de regressão multivariada foi realizada para calcular o risco de ICD, considerando possíveis confusões. **Resultados –** O risco de ICD em pacientes hospitalizados foi maior em indivíduos diagnosticados com doença inflamatória intestinal (OR: 4,44; IC95%: 4,35–4,52) e em pacientes que usavam clindamicina (OR: 1,55; IC95%: 1,53–1,57), antibióticos beta-lactâmicos (OR: 1,62; IC95%: 1,60–1,64), PPI (OR: 3,27; IC95%: 3,23–3,30), trazodona (OR: 1,31; IC95%: 1,29–1,33), nortriptilina (OR: 1,25; IC95%: 1,21–1,28) e mirtazapina (OR: 2,50; IC95%: 2,46–2,54). Depois de controlar as covariáveis, o risco de ICD não aumentou em pacientes que estavam tomando fluoxetina (OR: 0,94; IC95%: 0,92–0,96). **Conclusão –** Em contrário à fluoxetina; mirtazapina, nortriptilina e trazodona foram associados a um risco aumentado de ICD em pacientes hospitalizados.

Palavras-chave – Medicamentos antidepressivos, *Clostridioides difficile*, infecção por *Clostridioides difficile*.

REFERENCES

1. No authors listed. C difficile a rose by any other name. Lancet Infect Dis. 2019;19:449. doi:10.1016/S1473-3099(19)30177-X.
2. Rogers MA, Greene MT, Young VB, Saint S, Langa KM, Kao JY, et al. Depression, antidepressant medications, and risk of Clostridium difficileinfection. BMC Med. 2013;11:121. doi:10.1186/1741-7015-11-121.
3. Miller BA, Chen LF, Sexton DJ, Anderson DJ. Comparison of the Burdens of Hospital-Onset, Healthcare Facility-Associated *Clostridium difficile* Infection and of Healthcare-Associated Infection due to Methicillin-Resistant *Staphylococcus aureus* in Community Hospitals. Infect Control Hosp Epidemiol. 2011;32:387-90. doi:10.1086/659156.
4. McDonald LC, Owings M, Jernigan DB. *Clostridium difficile* Infection in Patients Discharged from US Short-stay Hospitals, 1996–2003. Emerg Infect Dis. 2006;12:409-15. doi: 10.3201/eid1205.051064.
5. Dalton BR, Lye-Maccannell T, Henderson EA, Maccannell DR, Louie TJ. Proton pump inhibitors increase significantly the risk of *Clostridium difficile* infection in a low-endemicity, non-outbreak hospital setting. Aliment Pharmacol Ther. 2009;29:626-34. doi:10.1111/j.1365-2036.2008.03924.x.
6. Siemann M, Koch-Dörfler M, Rabenhorst G, Institut PB. The clinical courses of 18 fatal cases. Intensive Care Med. 2000;26:416-21. doi: 10.1007/s001340051175.
7. Eze P, Balsells E, Kyaw MH, Nair H. Risk factors for Clostridium difficile infections – an overview of the evidence base and challenges in data synthesis. J Glob Health. 2017;7:010417. doi:10.7189/jogh.07.010417.
8. Brody DJ. Antidepressant Use Among Adults: United States, 2015–2018. NCHS Data Brief. 2020:8.
9. Giovannini S, Onder G, van der Roest HG, Topinkova E, Gindin J, Cipriani MC, et al. Use of antidepressant medications among older adults in European long-term care facilities: a cross-sectional analysis from the SHELTER study. BMC Geriatr. 2020;20:310. doi:10.1186/s12877-020-01730-5.
10. IBM Corporation. The IBM Explorys Platform: liberate your healthcare data. 2020. Available from: https://www. ibm.com/downloads/cas/4P0QB9JN.
11. Gaudet-Blavignac C, Foufi V, Bjelogrlic M, Lovis C. Use of the Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT) for Processing Free Text in Health Care: Systematic Scoping Review. J Med Internet Res. 2021;23:e24594. doi: **10.2196/24594**. Available from: https://www.jmir.org/2021/1/e24594/
12. Gaudet-Blavignac C, Foufi V, Bjelogrlic M, Lovis C. Use of the Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT) for Processing Free Text in Health Care: Systematic Scoping Review. J Med Internet Res. 2021;23:e24594. doi:26. doi:10.2196/24594.
13. Alkhayyat M. Epidemiology of neuroendocrine tumors of the appendix in the USA: a population-based national study (2014-2019). Ann Gastroenterol. 2021;34:713-20. doi:10.20524/aog.2021.0643.
14. Alkhayyat M, Qapaja T, Aggarwal M, Almomani A, Abureesh M, Al-Otoom O, et al. Epidemiology and risk of psychiatric disorders among patients with celiac disease: A population based national study. J Gastroenterol Hepatol. 2021;36:2165-70. doi:10.1111/jgh.15437.
15. Kelly CP, LaMont JT. *Clostridium difficile* — More Difficult Than Ever. N Engl J Med. 2008;359:1932-40. doi:10.1056/NEJMra0707500.
16. Szałach ŁP, Lisowska KA, Cubała WJ. The Influence of Antidepressants on the Immune System. Arch Immunol Ther Exp (Warsz). 2019;67:143-51. doi:10.1007/s00005-019-00543-8.
17. Jørandli JW, Thorsvik S, Skovdahl HK, Kornfeld B, Sæterstad S, Gustafsson BI, et al. The serotonin reuptake transporter is reduced in the epithelium of active Crohn's disease and ulcerative colitis. Am J Physiol-Gastrointest Liver Physiol. 2020;319:G761-G768. doi:10.1152/ajpgi.00244.2020.
18. Mann JJ. The Medical Management of Depression. N Engl J Med. 2005;353:1819-34. doi:10.1056/NEJMra050730.
19. Ghia J, Li N, Wang H, Collins M, Deng Y, El-Sharkawy RT, et al. Serotonin Has a Key Role in Pathogenesis of Experimental Colitis. Gastroenterology. 2009;137:1649-60. doi:10.1053/j.gastro.2009.08.041.
20. Gobin V, Van Steendam K, Denys D, Deforce D. Selective serotonin reuptake inhibitors as a novel class of immunosuppressants. Int Immunopharmacol. 2014;20:148-56. doi:10.1016/j.intimp.2014.02.030.
21. Taler M, Gil-Ad I, Lomnitski L, Korov I, Baharav E, Bar M, et al. Immunomodulatory effect of selective serotonin reuptake inhibitors (SSRIs) on human T lymphocyte function and gene expression. Eur Neuropsychopharmacol. 2007;17:774-80. doi:10.1016/j.euroneuro.2007.03.010.
22. Diamond M, Kelly JP, Connor TJ. Antidepressants suppress production of the Th1 cytokine interferon-γ, independent of monoamine transporter blockade. Eur Neuropsychopharmacol. 2006;16:481-90. doi:10.1016/j.euroneuro.2005.11.011.
23. DePestel DD, Aronoff DM. Epidemiology of *Clostridium difficile* Infection. J Pharm Pract. 2013;26:464-75. doi:10.1177/0897190013499521.