Antidepressants in functional gastrointestinal disorders: a review of recent clinical trials and possible mechanisms

Short title: Clinical application and mechanism of antidepressants in FGIDs

Jiaxin Wang†, Tianyu Liu†, Yan Zhao, Ye Zong, Peng Li*

Department of Gastroenterology, Beijing Friendship Hospital, Capital Medical University, Beijing 100050 China

†These authors have contributed equally to this work and share first authorship

*Correspondence: Peng Li: lipeng@ccmu.edu.cn

ABSTRACT

Functional gastrointestinal disorders (FGIDs), or disorders of brain-gut axis, is a common digestive problem, affecting about 20%-40% of the population. The high prevalence and unclear pathogenesis bring great difficulty to diagnosis and treatment, and cause significant influence and burden to patients and society. Antidepressants are typically used for FGIDs in clinical practice, which draw great attention, with satisfactory effect and safety. This article summaries the application of antidepressants in the treatment of FGIDs and the possible underlying mechanisms.

Keywords: Antidepressants, Functional gastrointestinal disorders, Disorders of brain-gut interaction, Treatment

INTRODUCTION

Functional gastrointestinal disorders (FGIDs) are the result of disorders of gut–brain

interaction. An FGID is a syndrome based on clinical symptoms that cluster together and diagnosed according to Rome criteria.[1] In a worldwide epidemiological survey involving 73,076 adults, 40.3% of Internet respondents and 20.7% of household interviewees reported suffering from symptoms of FGIDs.[2] Besides, those who met the Roman IV criteria seek for medical consult with intestinal problems twice as often as those without FGIDs.[2] FGIDs not only affect the patients' quality of life and their normal work, but also create huge social and economic burden.

FGIDs are related to complex combination of dysregulation in central nervous system (CNS) processing and gut function via the brain–gut axis, including turbulent motility, visceral hypersensitivity and mucosal, immune and gut microbiota alterations.[2] In addition, an FGID is related to psychosocial factors.[3]. Genetic, sociocultural and environmental factors can influence a person's psychosocial development at an early life stage, including personality traits, susceptibility to life stresses, psychological states, and cognitive and coping skills. These factors affect the susceptibility to gut dysfunction, directly or indirectly via the brain–gut axis.[4]

The most commonly studied psychological treatments for FGIDs are cognitive-behavior therapy (CBT), psychodynamic psychotherapy, and hypnosis. In terms of pharmacological treatment, gastrointestinal modifiers, anticholinergic agents, probiotics, anti-diarrheal agents, and intestinal secretagogues are effective to relieve the symptoms. Considering the presence of gut-brain interaction disorders, emerging evidence from clinical experience and accumulated effectiveness in other functional somatic syndromes make antidepressants considerable choice for FGIDs patients who fail to respond to first-line therapy. This article summaries the application of antidepressants in the treatment of FGIDs and the possible underlying mechanisms so as to explore a better treatment plan

GUT-BRAIN AXIS DYSREGULATION

Understanding the tight connection between the brain and the gut could help explain the reason why antidepressants are useful in some FGIDs. The gastrointestinal tract is controlled by a separate enteric nervous system (ENS), and linked to the CNS with bidirectional communication.[5] The gut contacts with the brain in two neuro-anatomical ways.[6] One is information exchange between the gut and brain directly through the autonomic nervous system (ANS) and vagus nerve (VN) in the spinal cord. The other is the mutual communication between the ENS in the gut and ANS and VN in the spinal cord.[6] The emotional-arousal brain circuit controls the output of the efferent ANS (positive/parasympathetic balance) and the stress hormone system (hypothalamic-pituitary-adrenal (HPA) axis), both of which alter gastrointestinal motility, immune or barrier function, thereby affecting visceral afferent signals.[7] In addition, neurotransmitters and neuro-effector drugs work in both the brain and gut.[8] Serotonin(5-HT), one of the most important neurotransmitters, plays a key role in the pathogenesis of irritable bowel syndrome (IBS), the most common FGIDs.[9] Reduction of brain 5-HT levels increases visceral perception and negative emotional bias in patients with IBS.[10] Gut microbiota plays a key part in stabilizing the intestine hemeostasis. The maturation of neuroendocrinology and the development of the gut immune system also depend on the gut microbiome, which influence the neural circuits and behaviors associated with stress response as well as immune function.[11-14] The smooth colonization of intestinal microorganisms is significant to the normal development of the HPA axis.[15] Correspondingly, stress and the HPA axis affect the composition of gut microbes.[16] Besides, gut bacteria are involved in the synthesis of neurotransmitters and

neuromodulators, such as 5-HT, butyric acid, and dopamine, which can be exchanged between microbial cells.[17-19] Diverse symptoms are related to an imbalance of microbes and dysregulation of inflammatory response in the gut.[20] Components of the bacteria themselves, like lipopolysaccharides (LPS), may also be released and have inflammatory activation effects on the host[21], which could sensitize the visceral afferent nerve and be related to dyskinesia.[22] In a study on gut microbiota and quality of life and depression, butyrate-producing Faecalibacterium and Coprococcus were consistently associated with higher quality of life indicators.[18]

POSSIBLE MECHANISMS OF ANTIDEPRESSANTS IN THE FGID*S*

Depression is a common comorbidity of mental illness in FGIDs. A meta-analysis estimated that the prevalence of depressive symptoms and disorders in IBS patients were 28.8% and 23.3%, respectively.[23] And depressive symptoms are reported notably more severe and more frequent in IBS patients compared with healthy controls.[24] Antidepressants are typically given to patients with moderate to severe disease severity, seriously impaired quality of life and other situation where regular treatment is not sufficient.[3] In North America antidepressants are reported in 30% to 55% of patients with FGIDs.[25, 26] Antidepressants are thought to treat gastrointestinal symptoms by modulating neurotransmitters such as 5-HT, norepinephrine and corticotropin-releasing factor, which help with the movement and sensation of the gut.[27] They also play an analgesic role by blocking receptors for serotonin, norepinephrine and several other neurotransmitters.[28] In addition, they reduce incoming visceral signals and may down-regulate incoming visceral signals by affecting anterior cingulate cortex function.[29, 30]

Studies have demonstrated structural changes in the brains of FGIDs.[31] Theories about neurogenesis suggest that antidepressants can restore lost neurons, as levels of brain-derived neurotrophic factor that predate neurogenesis have been found to rise with antidepressant treatment.[32, 33] Increased grey matter in the hypothalamus in patients with IBS may be associated with an association between IBS, stress, and the HPA axis.[34]

The choice of medication is influenced by diverse factors, including the main symptoms of consultants, severity of illness, presence of anxiety or depression comorbidities, prior use of similar medications, and preferences of the patient and doctor.[3] Low-dose tricyclic antidepressants (TCAs) can be used to treat chronic pain, with modes of action involving serotonin and norepinephrine, as well as such as blocking voltage-gated ion channels, opioid receptor activation and possible neuroimmune anti-inflammatory effects.[35, 36] Serotonin is able to activate over 15 receptor/receptor subtypes in the brain and gut. 5-HT3 receptor antagonists are used to treat functional diarrhea and 5-HT4 receptor agonists are used for functional constipation.[37] Selective serotonin reuptake inhibitors are not commonly used as monotherapies because of their poor efficacy in treating pain[3]. 5-HT3 antagonists could inhibit 5-HT3 receptors on endogenous and exogenous afferent fibers of mucosa and stimulate 5-HT3 receptors on inter neuronal and motor neurons, thus promoting fast formation of excitatory postsynaptic potential. This may be the mechanism by which the 5-HT3 antagonists reduce local progression and secretion of intestinal tract and alleviate diarrhea.[37] The visceral analgesic effect of 5-HT3 antagonist may be related to the role of 5-HT3 receptor in the activation of intestinal pain signal, and may also connected with the central mechanism of action.[38] Meanwhile, all cells of the intestinal mucosa virtually express the 5-HT4 receptor.[39] The 5-HT4 receptor antagonist can inhibit the secretion of 5-HT from chromaffin cells, mucus from goblet cells and chloride

ion from intestinal cells, thus alleviating diarrhea.[37] Selective serotonin reuptake inhibitors are a useful enhancer when used in combination with other drugs such as serotonin-norepinephrine reuptake inhibitors (SNRIs) or TCAs, or when patients have a high level of anxiety that directly contributes to their clinical presentation.[3] Considering the central role of serotonin and norepinephrine in down-regulating neural pathways, SNRIs may be an ideal class of drugs for regulating pain sensation.

A growing body of evidence support the role of antidepressants in the treatment of FGIDs, but there is still a gap in clear and definite mechanism, which requires further studies on the pathogenesis and treatment mechanisms of FGIDs.

EFFICACY AND SAFETY OF ANTIDEPRESSANTS IN THE TREATMENT OF FGIDS

Antidepressants included in existing clinical trials are TCAs, selective serotonin reuptake inhibitors (SSRIs), serotonin noradrenalin reuptake inhibitors (SNRIs) and tetracyclic antidepressants (TeCAs).[40] In 2018, the Rome Foundation working team (RFWT） report pointed out that low to modest doses of TCAs have sufficient evidence in the treatment of chronic gastrointestinal pain in FGIDs. SNRIs may have the same effect as TCAs but still need to be adequately tested. SSRIs can be considered if anxiety is the dominant clinical feature in addition to abdominal pain. As for tetracyclic antidepressants, no specific evaluation and recommendation has not been given due to limited studies.[41]

Here, we summarize the progress of clinical trials of antidepressants in FGIDs since 2018 to critically evaluate their application and efficacy.

TCAs

Among neuromodulators, low to moderate doses of TCAs are most recommended for the treatment of chronic gastrointestinal pain. In most studies, the dose range of TCA was 25-75 mg/d. There is insufficient evidence of analgesic effect at doses less than 25 mg. In addition, the TCA class of agents is the first-line treatment in central neuromodulater for treating IBS, particularly in IBS-D (irritable bowel syndrome with diarrhea). TCAs can be used in conjunction with proton pump inhibitor (PPI) in patients whose dyspeptic symptoms are consistent with epigastric pain syndrome (EPS).[41] In a single‐center, double‐blind, randomized controlled trial (RCT) in patients with functional dyspepsia (FD), 12-weeks treatment with imipramine 50mg per day relieved the global dyspepsia symptoms compared with placebo. But 18% patients in the imipramine group discontinued the study due to side effects such as dry mouth, constipation, drowsiness, insomnia, palpitations and blurred vision.[42] A multicenter, prospective RCT confirmed amitriptyline (50mg) can relieve FD symptoms and improve gastric accommodation.[43] In a post analysis of data from the clinical trial mentioned above, the reason for amitriptyline's effectiveness may be a modest improvement in patients' sleep.[44] A randomized double-blind placebo-controlled trial conducted by Kaosombatwattana *et al* reported that daily 10mg-nortriptyline treatment did not improve the life quality of patients diagnosed with FD.[45] In a recently published study, TCAs combined with diaphragmatic breathing/relaxation achieved a 90.9% improvement in clinical symptoms in patients with rumination syndrome.[46]

The above studies provided supporting evidence for RFWT's recommendation of TCAs' clinical application in FGIDs. A meta-analysis of drugs for functional dyspepsia

demonstrated that TCAs were ranked first when only high-quality studies were included.[47]

SSRIs

The RFWT report put forward a conclusion that SSRIs have no significant effect on visceral sensitivity in patients with FGIDs. However, SSRIs can still be considered in IBS if anxiety is present while the stomachache and diarrhea are not main symptoms.[41]

According to a retrospective study, combination of mosapride and fluoxetine can benefit patients with anxiety related to functional dyspepsia. The anxiety state, frequency of abdominal distention and defecation, and serum level of cholecystokinin in the combined treatment group were significantly lower than those in the mosapride alone group.[48] In a double-blind cross-over study, the citalopram administration was associated with higher upper esophageal sphincter post-swallow mean and maximum pressure values in healthy volunteers compared with placebo.[49] This study discovered the potential of citalopram as an anti-reflux treatment for FGIDs.

SNRIs

Duloxetine may be more practical in clinical use because of its lower median effective dose compared to venlafaxine, according to RFWT. Meanwhile, milnacipran is recommended to be considered if the patients can’t tolerate the other SNRIs’ adverse effects.[41]

Duloxetine is useful to treat the pain component in those diagnosed with central mediated abdominal pain syndrome (CAPS) related FGIDs based on findings from a

recently published RCT.[50] In this study, after 8 weeks of treatment, the proportion of patients in the duloxetine group who experienced a decrease in average pain scores of more than 50% was significantly higher than in the placebo group. However, there are currently no high-quality clinical trials of milnacipran for FGIDs

TeCAs

The tetracyclic antidepressants are recommended in the treatment of early satiety, nausea/vomiting, weight loss and disturbed sleep in FGIDs.[41] In 2018, a case report showed a 52-year-old woman diagnosed with IBS with predominant diarrhea, accompanied with depression and anxiety, improved in abdominal pain and diarrhea, after treatment of mirtazapine 30mg/day for one month.[51] Further clinical trials are needed for the evaluation of tetracyclic antidepressants in FGIDs.

BARRIER OF ANTIDEPRESSANTS IN THE TREATMENT OF FGIDS

A meta-analysis identified adverse events as the main cause of frequent discontinuation of antidepressants.[52] An investigation of American gastroenterologists about neuromodulators in IBS mentioned that concerns about side effects was the most common barrier of these agents' clinical application.[53] The reported side effects of antidepressants include drowsiness, dry mouth, constipation, sexual dysfunction, cardiovascular events, weight changes, agitation, diarrhea, night sweats, headache, nausea, dizziness, sleep disturbance, fatigue, and hepatotoxicity.[41] These side effects may be associated with their inhibition of serotonin uptake,[54] anticholinergic and antihistaminic actions.[55] More large-scale clinical studies are expected to evaluate the adverse events and provide

evidence for clinical treatment.

CONCLUSION

With the in-depth understanding of the biological and psychosocial mechanism of functional gastrointestinal disorders and gut-brain axis, functional gastrointestinal disorders are better defined as disorders of gut-brain interaction. Antidepressants can help relieve pain and regulate gastrointestinal motility and secretion by reducing visceral sensitivity and relaxing and smoothing the viscera.[56, 57] In addition, it also plays a role in common mental illness comorbidity by improving sleep and reducing pain.[58] There is a lack of specific guidance for the clinical use of antidepressants in FGIDs. Well-designed and high-quality clinical researches are much needed in the future

Conflict of Interest

None declared.

REFERENCES

1. Drossman DA, Hasler WL. Rome IV-Functional GI Disorders: Disorders of Gut-Brain Interaction. Gastroenterology. 2016; 150:1257-1261.

2. Sperber AD, Bangdiwala SI, Drossman DA *et al*. Worldwide Prevalence and Burden of Functional Gastrointestinal Disorders, Results of Rome Foundation Global Study. Gastroenterology. 2021; 160:99-114.

3. Van Oudenhove L, Crowell MD, Drossman DA *et al*. Biopsychosocial Aspects of Functional Gastrointestinal Disorders. Gastroenterology. 2016; 150:1355-1367.

4. Houghton LA, Heitkemper M, Crowell M *et al*. Age, Gender and Women's Health and

the Patient. Gastroenterology. 2016; 150:1332-1343.

5. Z A. Neurological and psychiatric aspects of some gastrointestinal diseases. Orv Hetil. 2008; 149:2079-2086.

6. Cryan JF, O'Riordan KJ, Cowan C *et al*. The Microbiota-Gut-Brain Axis. Physiol Rev. 2019; 99:1877-2013.

7. Mayer EA. The neurobiology of stress and gastrointestinal disease. Gut. 2000; 47:861-869.

8. Törnblom H, Drossman DA. Centrally targeted pharmacotherapy for chronic abdominal pain. Neurogastroenterol Motil. 2015; 27:455-467.

9. Holtmann GJ, Ford AC, Talley NJ. Pathophysiology of irritable bowel syndrome. Lancet Gastroenterol Hepatol. 2016; 1:133-146.

10. Labus JS, Mayer EA, Jarcho J *et al.* Acute tryptophan depletion alters the effective connectivity of emotional arousal circuitry during visceral stimuli in healthy women. Gut. 2011; 60:1196-1203.

11. Huo R, Zeng B, Zeng L *et al*. Microbiota Modulate Anxiety-Like Behavior and Endocrine Abnormalities in Hypothalamic-Pituitary-Adrenal Axis. Front Cell Infect Microbiol. 2017; 7:489.

12. Neufeld KM, Kang N, Bienenstock J *et al*. Reduced anxiety-like behavior and central neurochemical change in germ-free mice. Neurogastroenterol Motil. 2011; 23:255-264, e119.

13. Clarke G, Grenham S, Scully P *et al*. The microbiome-gut-brain axis during early life regulates the hippocampal serotonergic system in a sex-dependent manner. Mol Psychiatry. 2013; 18:666-673.

14. Chung H, Pamp SJ, Hill JA *et al*. Gut immune maturation depends on colonization

with a host-specific microbiota. Cell. 2012; 149:1578-1593.

15. Sudo N, Chida Y, Aiba Y *et al.* Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. J Physiol. 2004; 558:263-275.

16. Jahnke JR, Roach J, Azcarate-Peril MA *et al*. Maternal precarity and HPA axis functioning shape infant gut microbiota and HPA axis development in humans. Plos One. 2021; 16: e251782.

17. Ye L, Bae M, Cassilly CD *et al*. Enteroendocrine cells sense bacterial tryptophan catabolites to activate enteric and vagal neuronal pathways. Cell Host Microbe. 2021; 29:179-196.

18. Valles-Colomer M, Falony G, Darzi Y *et al*. The neuroactive potential of the human gut microbiota in quality of life and depression. Nat Microbiol. 2019; 4:623-632.

19. Forsythe P, Bienenstock J, Kunze WA. Vagal pathways for microbiome-brain-gut axis communication. Adv Exp Med Biol. 2014; 817:115-133.

20. Al BZ, Nitert MD, Mousa A *et al*. The Gut Microbiota and Inflammation: An Overview. Int J Environ Res Public Health. 2020;17.

21. Janssen AW, Kersten S. Potential mediators linking gut bacteria to metabolic health: a critical view. J Physiol. 2017; 595:477-487.

22. Spiller R, Garsed K. Postinfectious irritable bowel syndrome. Gastroenterology. 2009; 136:1979-1988.

23. Zamani M, Alizadeh-Tabari S, Zamani V. Systematic review with meta-analysis: the prevalence of anxiety and depression in patients with irritable bowel syndrome. Aliment Pharmacol Ther. 2019; 50:132-143.

24. Zhang QE, Wang F, Qin G *et al*. Depressive symptoms in patients with irritable bowel

syndrome: a meta-analysis of comparative studies. Int J Biol Sci. 2018; 14:1504-1512.

25. Drossman DA, Morris CB, Schneck S *et al.* International survey of patients with IBS: symptom features and their severity, health status, treatments, and risk taking to achieve clinical benefit. J Clin Gastroenterol. 2009; 43:541-550.

26. Ladabaum U, Boyd E, Zhao WK *et al.* Diagnosis, comorbidities, and management of irritable bowel syndrome in patients in a large health maintenance organization. Clin Gastroenterol Hepatol. 2012; 10:37-45.

27. Gershon MD, Tack J. The serotonin signaling system: from basic understanding to drug development for functional GI disorders. Gastroenterology 2007; 132:397-414.

28. Tracey I, Mantyh PW. The cerebral signature for pain perception and its modulation. Neuron. 2007; 55:377-391.

29. Drossman DA. Beyond tricyclics: new ideas for treating patients with painful and refractory functional gastrointestinal symptoms. Am J Gastroenterol. 2009; 104:2897-2902.

30. Morgan V, Pickens D, Gautam S *et al*. Amitriptyline reduces rectal pain related activation of the anterior cingulate cortex in patients with irritable bowel syndrome. Gut. 2005; 54:601-607.

31. Kano M, Dupont P, Aziz Q *et al*. Understanding Neurogastroenterology from Neuroimaging Perspective: A Comprehensive Review of Functional and Structural Brain Imaging in Functional Gastrointestinal Disorders. J Neurogastroenterol Motil. 2018; 24:512-527.

32. Brunoni AR, Lopes M, Fregni F. A systematic review and meta-analysis of clinical studies on major depression and BDNF levels: implications for the role of neuroplasticity in depression. Int J Neuropsychopharmacol. 2008; 11:1169-1180.

33. Colucci-D'Amato L, Speranza L, Volpicelli F. Neurotrophic Factor BDNF, Physiological Functions and Therapeutic Potential in Depression, Neurodegeneration and Brain Cancer. Int J Mol Sci. 2020;21.

34. Blankstein U, Chen J, Diamant NE *et al*. Altered brain structure in irritable bowel syndrome: potential contributions of pre-existing and disease-driven factors. Gastroenterology. 2010; 138:1783-1789.

35. Dharmshaktu P, Tayal V, Kalra BS. Efficacy of antidepressants as analgesics: a review. J Clin Pharmacol. 2012; 52:6-17.

36. Finnerup NB, Attal N, Haroutounian S *et al*. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol. 2015; 14:162-173.

37. Mawe GM, Hoffman JM. Serotonin signalling in the gut--functions, dysfunctions and therapeutic targets. Nat Rev Gastroenterol Hepatol. 2013; 10:473-486.

38. Del CA, Israelyan N, Gross MK. Novel aspects of enteric serotonergic signaling in health and brain-gut disease. Am J Physiol Gastrointest Liver Physiol. 2020; 318: G130-G143.

39. Hoffman JM, Tyler K, Maceachern SJ *et al*. Activation of colonic mucosal 5-HT(4) receptors accelerates propulsive motility and inhibits visceral hypersensitivity. Gastroenterology. 2012; 142:844-854.

40. Tornblom H, Drossman DA. Psychotropics, Antidepressants, and Visceral Analgesics in Functional Gastrointestinal Disorders. Current gastroenterology reports. 2018; 20:58.

41. Drossman DA, Tack J, Ford AC *et al.* Neuromodulators for Functional Gastrointestinal Disorders (Disorders of Gut−Brain Interaction): A Rome Foundation Working Team Report. Gastroenterology. 2018; 154:1140-1171.

42. Cheong PK, Ford AC, Cheung CKY *et al*. Low-dose imipramine for refractory

functional dyspepsia: a randomised, double-blind, placebo-controlled trial. Lancet Gastroenterol Hepatol. 2018; 3:837-844.

43. Lacy BE, Saito YA, Camilleri M *et al*. Effects of Antidepressants on Gastric Function in Patients with Functional Dyspepsia. Am J Gastroenterol 2018; 113:216-224.

44. Herrick LM, Camilleri M, Schleck CD *et al*. Effects of Amitriptyline and Escitalopram on Sleep and Mood in Patients with Functional Dyspepsia. Clin Gastroenterol H 2018; 16:401.

45. Kaosombatwattana U, Pongprasobchai S, Limsrivilai J *et al*. Efficacy and safety of nortriptyline in functional dyspepsia in Asians: A randomized double-blind placebo-controlled trial. J Gastroen Hepatol. 2018; 33:411-417.

46. Robles A, Romero YA, Tatro E *et al.* Outcomes of Treating Rumination Syndrome with a Tricyclic Antidepressant and Diaphragmatic Breathing. Am J Med Sci. 2020; 360:42-49.

47. Ford AC, Moayyedi P, Black CJ *et al.* Systematic review and network meta-analysis: efficacy of drugs for functional dyspepsia. Aliment Pharm Ther. 2021; 53:8-21.

48. Wang Y, Wang M, Li Y. Effects of a combination of moxapride and fluoxetine on gastrointestinal function in patients with functional dyspepsia-associated anxiety. Trop J Pharm Res. 2021; 20:1293-1298.

49. Manolakis AC, Broers C, Geysen H *et al.* Effect of citalopram on esophageal motility in healthy subjects-Implications for reflux episodes, dysphagia, and globus. Neurogastroenterol Motil. 2019; 31: e13632.

50. Wang Y, Xu T, Qiao Y *et al.* Efficacy of Duloxetine in Treatment of Central Mediated Abdominal Pain Syndrome. 2020; 25:666-669.

51. Akama F, Mikami K, Watanabe N *et al.* Efficacy of Mirtazapine on Irritable Bowel

Syndrome with Anxiety and Depression: A Case Study. J Nippon Med Sch. 2018; 85:330-333.

52. Xiong N, Duan Y, Wei J *et al.* Antidepressants vs. Placebo for the Treatment of Functional Gastrointestinal Disorders in Adults: A Systematic Review and Meta-Analysis. Front Psychiatry. 2018;9.

53. Nulsen B, Lebrett W, Drossman DA *et al.* A survey of gastroenterologists in the United States on the use of central neuromodulators for treating irritable bowel syndrome. Aliment Pharm Ther. 2021; 54:281-291.

54. C A, S S, Kb C *et al.* Serotonin reuptake inhibitor antidepressants and abnormal bleeding: a review for clinicians and a reconsideration of mechanisms. The Journal of clinical psychiatry. 2010; 71:1565-1575.

55. Sp R, M M. Pharmacologic treatment of depression in patients with heart disease. Psychosom Med. 2005: S54-S57.

56. Sobin WH, Heinrich TW, Drossman DA. Central Neuromodulators for Treating Functional GI Disorders: A Primer. Am J Gastroenterol. 2017; 112:693-702.

57. Mikocka-Walus A, Ford AC, Drossman DA. Antidepressants in inflammatory bowel disease. Nat Rev Gastroenterol Hepatol. 2020; 17:184-192.

58. Frolkis AD, Vallerand IA, Shaheen AA *et al.* Depression increases the risk of inflammatory bowel disease, which may be mitigated by the use of antidepressants in the treatment of depression. Gut. 2019; 68:1606-1612.