# Words of Editor-in-Chief

*Psychosomatic Gastroenterology* (PG) is the official academic journal of Chinese Digestive Psychosomatic Union (CDPU), which was founded in April 2016 in Shanghai, China. It is the first global journal focusing on "psychosomatic gastroenterology".

*Psychosomatic Gastroenterology* is an open access, peer-reviewed journal that covers basic and clinical research, therapeutics and education for all aspects of psychosomatic gastroenterology, including the mechanism research and therapeutic research. The accepted articles include original research, reviews, case reports, expert experience, academic event reports and so on. *Psychosomatic Gastroenterology* creates a novel interface between the fields of social, psychological and biological research.

We hope *Psychosomatic Gastroenterology* would play an important role in promoting the management of gastrointestinal diseases in which psychological mechanisms may be involved. And, we look forward to publishing more and more your papers with great importance in psychosomatic gastroenterology.

Chairman of Chinese Digestive Psychosomatic Union
Chief of Chinese Association of Psychosomatic Digestive Diseases
Professor of Department of Gastroenterology

©Psychosomatic Gastroenterology. All rights reserved.

# Table of Contents

VOL 5, NO 1 Jun 2022



©Psychosomatic Gastroenterology. All rights reserved.

# To improve clinical outcomes of refractory gastrointestinal disorders by targeting the gut-brain interaction

**Bi-Yu Wu, Sheng-Liang Chen***
**Division of Gastroenterology and Hepatology, Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai Institute of Digestive Disease, Chinese Digestive Psychosomatic Union, Shanghai, China**

**Abstract:** The incidence of gastrointestinal (GI) diseases associated with psychological factors, dietary behavior, and gut microbiota, such as functional GI diseases (FGIDs) and inflammatory bowel diseases (IBD), is increasing. A proportion of these disorders are unresponsive to the regular GI medications, and thus defined as refractory gastroesophageal reflux disease (rGERD), functional dyspepsia (rFD), irritable bowel syndrome (rIBS), and GI dysmotility (including gastroparesis and recurrent nonorganic incomplete ileus), and inflammatory bowel disease (rIBD). It has become a great challenge in clinical practice, causing a large social and medical burden. Recently, the role of dysregulated gut-brain interaction in the pathogenesis of GI disorders has attracted much attention of researchers. Their studies have revealed a couple of new potential targets, which are expected to improve the therapeutic effect. Based on this background, this mini-review mainly addressed the application of neuromodulators (NMs) for disorders of gut-brain interaction (DGBI). Medications targeting the key process of gut-brain axis and GI pathophysiology were also discussed.

***Key words:*** refractory functional gastrointestinal disorders; gut-brain interaction; neuromodulator

Correspondence to:
Prof. Sheng-Liang Chen
145 Middle Shandong Road, Shanghai 200001, China
E-mail: slchenmd@hotmail.com
Tel.: 86 21 63200784; Fax: 86 21 63266027

©Psychosomatic Gastroenterology. All rights reserved.
Recieved 14 February, accepted 15 May

## Introduction

Nowadays, with the great changes in natural environment and the acceleration of social and economic development, the incidence of gastrointestinal (GI) diseases associated with psychological factors, dietary behavior, and gut microbiota, such as functional GI diseases (FGIDs) and inflammatory bowel diseases (IBD), is increasing. However, traditional medications for digestive diseases cannot prevent the key pathophysiological processes. Thus, a proportion of patients become refractory cases due to the unresponsiveness to traditional agents. In recent years, the pandemic of coronavirus disease 2019 (COVID-19) has exacerbated this situation. Although endoscopy and molecular biology techniques have made great progress, they seem to contribute little to the clinical outcomes of the refractory GI disorders, which include refractory gastroesophageal reflux disease (rGERD), functional dyspepsia (rFD), irritable bowel syndrome (rIBS), and GI dysmotility (including gastroparesis and recurrent nonorganic incomplete ileus), and inflammatory bowel disease (rIBD). It has become a great challenge in clinical practice, causing a large social and medical burden.

In recent years, great progresses have been made in the understanding of the role of dysregulated gut-brain interaction in the pathogenesis of GI disorders. Researches have revealed a couple of new targets which may be helpful in improvement of the clinical outcomes of refractory GI disorders. Based on this background, this review mainly addressed the application of neuromodulators (NMs) for disorders of gut-brain interaction (DGBI) and medications targeting the key process of gut-brain axis and GI pathophysiology.

## Application of neuromodulators

The Rome Foundation of FGIDs recommends that the traditional "central nervous drugs", "psychotropic drugs", and "antianxiety or antidepressive agents" are referred to as NMs to facilitate the understanding of DGBI and the appropriate selection of medications by gastroenterologists in clinical practice. The use of NMs also helps to reduce patients' stigma towards the disease and medications, thus improving doctor-patient communication and achieving better compliance. Although there is a consensus for the necessity of NMs in the treatment of DGBI, a recent study on the application of NMs by gastroenterologists showed a lack of theoretical and practical guidance in the selection of NMs, drug combination, dose adjustment, and course determination. Poor compliance caused by patients' stigma is the biggest obstacles for the use of NMs [1]. Understanding the pathogenesis of DGBI as well as learning from traditional Chinese medicine (TCM) may bring light to the solution of these problems.

### *Targets at the brain-to-gut axis*

So far, there have been abundant researches on abnormalities of the brain functioning areas as initiating factors to trigger and aggravate GI disorders [2]. The relationship between different psychological factors and the corresponding brain functioning areas and that between brain functioning areas and GI manifestations have been largely elucidated. Identifying these relationships is the key to properly select NMs and drug combination regimen.

### *The choice of NMs*

On the whole, there are two kinds of psychological stress affecting the specific brain functioning areas and the subsequent GI manifestations. The first type is emotional stress, most of them beginning with a transient stress event in life, such as emotional conflicts, death of family members, changes in interpersonal relationships and work status, and so on. The affected brain functioning areas include the prefrontal lobe, cingulate gyrus (especially anterior cingulate gyrus), insula and hippocampus. Activation of the central-peripheral (autonomic nervous system and spinal nerves) neural network and humoral (neuroendocrine) system can cause abnormal sensory response, motility disorders, mucosal immune dysfunction and inflammatory reactions of GI tract.

Clinically, the activation of the above pathway can cause two opposite emotional manifestations: (1) The positive emotional manifestations such as anxiety and irritability, which are associated with the activation of brain functioning areas (such as the prefrontal lobe, cingulate gyrus, and insula) and the inhibition of the midbrain analgesic nuclei, as well as the up-regulation of the spinal cord pain reflex. Through the hypothalamus-pituitary-adrenal axis, the up-regulated


©Psychosomatic Gastroenterology. All rights reserved.

efferent impulses of autonomic nerves stimulate neuroendocrine system. In accordance with that, GI abnormalities are usually visceral hypersensitivity, discordance, and enhancement of motor and secretory functions (such as gastroesophageal reflux, peptic ulcer, borborygmus and diarrhea). Immune irritation and mucosal inflammatory response can also coexist. For such psychosomatic GI abnormalities, NMs with sedation and antianxiety effect are appropriate. The medications include tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) such as fluvoxamine, paroxetine and duloxetine. On one hand, these NMs directly improve the emotional problems via the central action, and through the brain-to-gut interaction, they can also abrogate the GI irritation. On the other hand, they can elevate the level of 5-hydroxytryptamine (5-HT) and other excitatory neurotransmitters in GI mucosa and exert the anticholinergic effect, leading to the inhibition of GI movement and excessive secretion. (2) On the contrary, the negative emotional manifestations (such as depression) are usually associated with the decreased excitability of the prefrontal lobe, cingulate gyrus, and insula. In accordance with that, GI abnormalities are manifested as the ambiguity of discomfort (such as inaccurate location, difficulty to describe the characteristics, etc.), and dysfunction of motility and secretion (such as loss of appetite, postprandial fullness, dry stools, inadequate defecatory propulsion, etc.), with concurrent mild mucosal inflammation. In this case, it is appropriate to choose powerful antidepressive NMs (such as fluoxetine, sertraline, citalopram, venlafaxine, etc.), which mainly promotes central emotional depression and up-regulates GI functions through the brain-to-gut interaction.

The second type of psychological stress affecting the specific brain functioning areas is the changes of thinking model and biorhythms, commonly seen in teenagers with more mental conflicts and workers with long-term and high intensity of logical thinking (such as computer programming, financial analysis, scientific research, etc). This type of stress also contains a chronic sense of fear triggered by the pressure from natural or mental environment, such as high-risk work, positions with great responsibility, etc. Drug addiction and circadian rhythm disorders can be included as well. Accordingly, the involved brain functioning areas are the orbitofrontal cortex, the striatum, the ventral tegmental area of the midbrain, the suprachiasmatic nucleus, and the amygdala. The abnormalities of these areas usually cause paranoid sensations (such as glous hystericus, foreign-body sensation in abdomen, and anal distensibility, etc.) and cognitive anomalies of etiology, diagnosis and treatment (including paranoia, difficulty in communication, and hypochondriasis). For such problems, multi-target NMs with complex mechanisms, such as antidepressants with anti-5-HT2 effect, atypical antipsychotics, biorhythm regulator, sedatives, and so on, should be chosen.

### *The combination of NMs*

Clinically, the two types of psychological stress and corresponding GI manifestations often coexist and appear alternately. This phenomenon may be due to the complex connections between the brain functioning areas in the process of evolution [1]. The areas that control emotions (the cortex) and cognitive thinking (the limbic system) are functionally linked, and they affect each other to maintain the homeostasis of the body (such as immunity, metabolism and biorhythm, etc.). So the combination of NMs is necessary. To this end, appropriate antidepressants are usually selected in the treatment of GI disorders caused by the first type of psychological stress, while the so-called " synergist " is used in treatment of GI disorders caused by the second type. The term "synergist" is used by psychiatrists to refer to a drug that has no obvious antidepressive effect on its own, but can increase the efficacy of an antidepressant. To date, clinical studies have shown that the efficacy of multi-targeted TCAs is not inferior to other antidepressants and they are still the most widely used NMs in the treatment of DGBI. In China, the combination of low-dose TCAs and low-dose atypical antipsychotic drugs has good efficacy in treating psychosomatic digestive diseases, and has been widely used [1,3].

### *The dosage and course of NMs*

Different from psychiatrists, the problems faced by GI specialists are GI disorders but not psychological disorders. Therefore, the type, dosage and course of NMs are different [4]. The use of NMs in psychosomatic digestive disorders can be summarized into three situations:

©Psychosomatic Gastroenterology. All rights reserved.

(1) during solving psychological problems, the GI adverse reactions should be avoided or reduced [5,6]. Pay attention to the dosage in this case, because most of the therapeutic effects are dose-dependent and better efficacy means a greater tendency to adverse reactions. The course of treatment need to follow the guidelines of psychiatry. After a full course of treatment (generally >6 months) during which the therapeutic effect is maintained, the drug should be gradually withdrawn. (2) GI disorders are the main reason for consultation and clinical treatment target, accompanied by psychological abnormalities that have not yet reached the diagnostic criteria for psychological diseases. In this case, the selection of NMs should take into account the pathophysiological mechanism of psychiatric and GI disorders. It is advisable to start with a low dose and gradually increase to a dose with satisfactory therapeutic effect. The longer the time to response, the longer the process of maintenance and withdrawal period. (3) There are no psychological problems that can be diagnosed or identified, but the regular treatment regimens for GI disorders cannot achieve satisfactory outcomes. Low doses of NMs can be tried in this case. The underlying mechanism may be associated with the direct action on peripheral nerves and/or the GI tract. Treatment course can also refer to the drugs commonly used for GI discomfort.

### *Targets at the gut-to-brain axis*

The concepts of "leaky gut" and "leaky gut syndrome" are the most prominent progress in the regulation of gut-to-brain interaction [7]. Changes in the natural environment, improper dietary behavior, the imbalance of body nutrition, and GI infection can lead to the changes in the physicochemical environment of intestinal lumen, the imbalance of microecology, weakening of the intestinal mucosal barrier, and the increase of permeability. These changes facilitate the breakthrough of harmful foods, drugs, microorganisms and their products from the intestinal mucosal barrier to enter the circulation and CNS, contributing to the occurrence of systemic inflammatory response syndrome (SIRS) and more seriously the multiple organ dysfunction syndrome (MODS).

The therapeutic targets related to "leaky gut syndrome" mainly include: (1) The improvement of intestinal microecology using the probiotics and antibiotics that are not absorbed by the intestine. Some studies have shown the therapeutic effect of probiotics, whereas the selection of probiotics and the dosage and course should be individualized. For example, studies on the treatment of IBS with probiotics have revealed that the efficacy is dose-dependent, and the course of treatment generally needs more than 4 weeks, and the best efficacy is reached within 8 to 10 weeks. In addition, the effect of probiotics can be extended for 4 weeks after withdrawal [8]. However, there is still insufficient evidence to reach a consensus on the indications and duration of the antibiotics unabsorbable by the intestine. (2) The improvement of inflammatory reactions. Cyclooxygenase-1 (COX-1) inhibitors, leukotriene receptor antagonists, inflammatory cell stabilizers, histamine (H1/2) receptor blockers, 5-aminosalicylic acid, monoclonal antibodies targeting cytokines, and glucocorticoids (such as budesonide) have been reported in some studies, but more research is needed in the future [9]. (3) Improving the integrity and defensive function of the intestinal mucosa [10].

## New targets at GI pathophysiology

The esophageal dysmotility is one of the new targets for the management of esophageal diseases. The dysmotility in the esophageal body and the lower esophageal sphincter (LES) is of the greatest clinical significance. For example, increased ineffective movement in the clearance of the esophageal content in the esophageal body and decreased LES resting pressure are associated with the occurrence of GERD, while LES achalasia and lack of smooth muscle peristalsis in the esophageal body are associated with achalasia [11]. However, the classic prokinetic drugs (such as 5-HT4 receptor agonists, dopamine D2 antagonists, anti-LES transient relaxation agents, etc.) have not obtained satisfactory therapeutic effect. In clinical practice, the author's team has realized that these two kinds of motility disorders are respectively related to the positive and negative emotional factors mentioned above, and NMs may be effective (unpublished). Moreover, receptor sensitization of the esophagus to physicochemical damage is another important target [12]. These receptors usually include capsaicin receptor (transient receptor potential


©Psychosomatic Gastroenterology. All rights reserved.

vanilloid, TRPV), adenosine triphosphate (ATP) receptor P2X, adenosine receptors A1, A2α, and 5-HT3 receptors, whereas antagonists of these receptors are rarely used in the treatment of esophageal visceral hypersensitivity. Since the sensitivity of these receptors is pH-dependent, and the sensitivity increases when pH <5.5, the enhancement of acid suppression may obtain better therapeutic effect.

Moreover, improving gastric sensitivity is one of the targets for dealing with GI disorders. The pacemaker of the slow-wave rhythm of GI motility is located in the proximal 1/4 to 1/3 of the greater curvature of stomach, and postprandial gastric filling triggers acceleration of distal intestinal motility (defined as gastro-colic reflex). Therefore, acid suppressive therapy has been used to relieve diarrhea and IBS symptoms associated with meals [13].

In addition, duodenal inflammation is a new target for the treatment of GI diseases that deserves great attention [14,15]. While the duodenum responds to gastric emptying, it can resist, and even reverse peristalsis and reflux the contents to stomach and/or esophagus. The duodenum, which is connected to the biliary tract and pancreas through the sphincter of Oddi, primarily determines the efficiency of digestion and absorption. Therefore, it affects food composition, microecology and metabolites in distal intestinal lumen, and indirectly affects mucosal infection and immune homeostasis. Duodenal inflammation, together with the "leaky gut" related central nervous system (CNS)-enteric nervous system (ENS) interaction disorders and gastroduodenal-Oddi sphincter motility disorders, plays an important role in the overlapping and refractory symptoms of FGIDs, IBD and chronic liver diseases. Promising targets for duodenal inflammation include acid suppression drugs, monoclonal antibodies targeting cytokines, budesonide, anti-CRTH2 (chemoattractant receptor homologue expressed on Th2 cells), histamine (H1/2) receptor blockers, leukotriene receptor antagonists, 5-HT3 receptor antagonists, local anesthetic agents, nutrients for epithelial tight junction, probiotics, and unabsorbable antibiotics [14,15].

Regarding the therapeutic targets of the distal intestinal tract, the hotspots in recent years are microecological imbalance, increased mucosal permeability and motility disorders. There have been many reports and literatures, thus they will not be discussed here.

## Conclusions

In this mini-review, we discussed the application of neuromodulators (NMs) for DGBI to regulate but-brain interacton. Via acting on the new potential targets at the brain –gut axis to modulate the functioning of CNS and peripheral nervous system, NMs are capable of regulating the positive and negative emotional manifestations and thus alleviate refractory GI symptoms. The choice of proper NMs and determination of dosage and treatment course are pivotal for the clinical outcomes of refractory GI disorders. Medications targeting the key process of gut-brain axis and GI pathophysiology were also discussed. Probiotics, unabsorbed antibiotics, and anti-inflammatory agents were recommended.

## Conflicts of interest statement

None declared.

## References

1. 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 Pharmacol Ther. 2021;54:281-291.
2. Weltens N, Iven J, Van Oudenhove L, et al. The gut-brain axis in health neuroscience: implications for functional GI disorders and appetite regulation. Ann N Y Acad Sci. 2018;1428:129-150.
3. Zhang Y, Becker T, Kösters M. Preliminary study of patterns of medication use for depression treatment in China. Asia Pac Psychiatry. 2013;5:231-236.
4. Drossman DA, Tack J, Ford AC, et al. Neuromodulators for Functional GI Disorders (Disorders of Gut-Brain Interaction): A Rome Foundation Working Team Report. Gastroenterology. 2018;154:1140-1171.e1.
5. Chen SL. A review of drug therapy for functional dyspepsia. J Dig Dis. 2013;14:623-625.
6. Luo QQ, Chen SL. Use of neurotransmitter regulators in functional GI disorders based on symptom analysis. J Dig Dis. 2017;18:203-206.
7. Camilleri M. Leaky gut: mechanisms, measurement

©Psychosomatic Gastroenterology. All rights reserved.

and clinical implications in humans. Gut. 2019;68:1516-1526.
8. Ford AC, Harris LA, Lacy BE, et al. Systematic review with meta-analysis: the efficacy of prebiotics, probiotics, synbiotics and antibiotics in irritable bowel syndrome. Aliment Pharmacol Ther. 2018;48:1044-1060.
9. Wauters L, Talley NJ, Walker MM, et al. Novel concepts in the pathophysiology and treatment of functional dyspepsia. Gut. 2020;69:591-600.
10. Kinashi Y, Hase K. Partners in Leaky Gut Syndrome: Intestinal Dysbiosis and Autoimmunity. Front Immunol. 2021;12:673708.
11. Yadlapati R, Kahrilas PJ, Fox MR, et al. Esophageal motility disorders on high-resolution manometry: Chicago classification version 4.0. Neurogastroenterol Motil. 2021;33:e14058.
12. Gyawali CP, Fass R. Management of Gastroesophageal Reflux Disease. Gastroenterology. 2018;154:302-318.
13. Simrén M, Abrahamsson H, Björnsson ES. An exaggerated sensory component of the gastrocolonic response in patients with irritable bowel syndrome. Gut. 2001;48:20-27.
14. Wauters L, Burns G, Ceulemans M, et al. Duodenal inflammation: an emerging target for functional dyspepsia? Expert Opin Ther Targets. 2020;24:511-523.
15. Wauters L, Ceulemans M, Frings D, et al. Proton Pump Inhibitors Reduce Duodenal Eosinophilia, Mast Cells, and Permeability in Patients With Functional Dyspepsia. Gastroenterology. 2021;160:1521-1531.e9.


©Psychosomatic Gastroenterology. All rights reserved.