# 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".

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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
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# Table of Contents

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# Expert consensus on clinical management of digestive disorders with disrupted biorhythm

**Chinese Digestive Psychosomatic Union**

**Abstract:** Biorhythm such as sleep-wake, resting-activity, dietary intake, hormone secretion, temperature and blood pressure fluctuation affects pathophysiological processes of the digestive system. Disturbances of biorhythm, especially circadian rhythm, are associated with the development, progress and outcome of digestive diseases. Reconstructing of normal biorhythm is of great significance for the maintaining of gut health. However, consensus on the management of digestive diseases with comorbid biorhythm disorders is currently lacking. The Chinese Digestive Psychosomatic Union organized experts to form a consensus on clinical management of digestive disorders with disrupted biorhythm based on systemic review of research progress and clinical experience. The consensus contained 21 statements. Each statement with evidence-based medicine grade and interpretations was reported.

***Key words:*** biorhythm; circadian rhythm; digestive diseases; functional gastrointestinal disorders; digestive psychosomatic disorders; melatonin; melatonin receptor agonists

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## Introduction

With the development of society and economy, the incidence of gastrointestinal (GI) diseases related to environmental factors (e.g., psychological stress, circadian rhythm, dietary behavior, and microorganisms) such as functional GI disorders (FGIDs) and inflammatory bowel disease (IBD) is rising and becoming a challenge to people health. Recent research on gut-brain interaction has given digestive physicians a deeper understanding of the bidirectional regulation between gut and psychological factors (such as biorhythm) [1]. In recent years, it is accepted that neuromodulators (mainly antidepressants and antianxiety drugs) benefit in the treatment of digestive disorders. However, how to manage digestive diseases with comorbid biorhythm disorders is still unexperienced and consensus on such clinical issues are still lacking.

In recent years, clinical research on the reconstruction of normal biorhythm to alleviate GI symptoms is emerging, which may be helpful for the evaluation and management of digestive diseases. Based on the relevant literature in Medline, Embase, Cochrane and China Science Periodical Database (CSPD), 37 national experts from Chinese Digestive Psychosomatic Union reached 21 statements combined with their own clinical experience. The quality of evidence referred to the grading method of U.S. Preventive Services Task Force (USPSTF) [2]: I: Evidence from a Meta-analysis containing randomized controlled trials, or at least from one well-designed randomized controlled trial; IIa: Evidence from well-designed non-randomized controlled trials ; IIb : Evidence from well-designed cohort studies or case-control studies (preferably multi-center studies); IIc: Evidence from time-series studies with or without an intervention, or from non-controlled trials with significant differences; III: Evidence from empirical experience, descriptive studies, or expert committee reports. Recommendation grading standard: A: High quality evidence supporting the statement; B: General evidence supporting the statement; C: Weak evidence supporting the statement; D: General evidence that doesn't support or refuting the statement; E: High quality evidence that doesn't support or refuting the statement. Each recommendation in the guideline was approved with the agreement of more than 80% of the participants.

## Overview of the relationship between biorhythm disruption and digestive diseases

*Statement 1: Common manifestations of biorhythm disorders include abnormalities in sleep-wake, resting-activity, dietary intake, hormone secretion, temperature and blood pressure fluctuation. In brain, biorhythm is regulated by the suprachiasmatic nucleus (SCN) in the hypothalamus.*

Evidence grade: I; Recommendation grade: A; Statement consent rate: 100%.

Biorhythm refers to rhythmic changes of all activities in life. Depending on the cycle time, biorhythms can be divided into circadian, lunar, and circannual rhythm [3]. The physiological basis for generating and maintaining biorhythms includes central and peripheral rhythm systems as well as input and output systems. Central rhythm system is mainly regulated by SCN. Upon sensed by the input system, environmental signals (e.g., the light signals) are transmitted to the central circadian clock. The latter transmits the signals to the peripheral rhythm organs through the output system to maintain the physiological activities of the body. The inherent biorhythm of the human body is influenced by a variety of internal and external factors such as living habits, psychological condition and physical diseases. Biorhythm disturbances can manifest as abnormalities in sleep-wake, resting-activity, dietary intake, hormone secretion, temperature and blood pressure fluctuation [4].

*Statement 2: Biorhythm disorders can influence gut function, and thus could be the cause of digestive diseases.*

Evidence grade: IIa; Recommendation grade: A; Statement consent rate: 100%.

With people's lifestyle changes (such as shift-work, staying up late, irregular diet, emotional problems, etc.), biorhythm disorders have become very common. Among them, the most intensively studied is disorder of the circadian rhythm (the body function changes within a period of nearly 24 h), mainly manifesting as the sleep-wake rhythm disturbance. It has been shown that biorhythm dysregulation may lead to

metabolic diseases (e.g. diabetes and obesity), tumors, neurodegenerative diseases and other chronic diseases [3,4], and even increase the risk of cardiovascular and stroke-related death [4-6]. Gut function such as gastric acid secretion, intestinal nutrient absorption, motor function, and flora homeostasis is also regulated by biorhythms [7-8]. Digestive disorders are often accompanied by biorhythm disturbance, such as acid reflux, dyspepsia, irregular defecation and other clinical symptoms that do not conform to the normal rhythm, and abnormal sleep-wake rhythm [7].

### *Statement 3: Biorhythm disorders are often comorbid with psychological disorders, and participate synergistically to the pathogenesis of digestive psychosomatic diseases.*

Evidence grade: IIc; Recommendation grade: A; Statement consent rate: 100%.

Disruption of sleep-wake rhythm is one of the major causes for depression, anxiety, and sleep disorders. Epidemiological surveys have shown that about 50% - 90% of patients with depression have complaints of sleep disorders [9]. Biorhythm disruption is one of the important clinical features and pathophysiological mechanisms of depression [10,11]. Patients with digestive psychosomatic diseases also have complaints of sleep disorders and psychological disorders, suggesting that biorhythm dysregulation and psychological factors jointly participate to the pathogenesis of digestive psychosomatic diseases.

### *Statement 4: FGIDs (disorders of gut-brain interaction) are often accompanied by biorhythm disorders.*

Evidence grade: IIc; Recommendation grade: A; Statement consent rate: 94.6%.

A survey on 931 patients with FGIDs in the gastroenterology outpatient department of 6 hospitals in Tianjin showed that 69.9% of the patients suffer from sleep disorders [12]. Another survey showed that the hospitalized patients with GI tumors or FGIDs display the highest incidence of sleep disorders, which is 82.6% and 81.2%, respectively [13]. In addition, the incidence of irritable bowel syndrome (IBS) was significantly higher in rotating shift workers than in day shift workers (48% *vs*. 31%, $P < 0.01$) . A community-based cross-sectional study showed a positive correlation between GI symptoms and sleep disorders (adjusted OR = 1.29, 95% CI: 1.22-1.36) [15].

## Pathogenesis

### *Statement 5: Sleep disorders affect gastric acid secretion and are associated with acid-related diseases.*

Evidence grade: IIc; Recommendation grade: A; Statement consent rate: 100%.

Human gastric acid secretion has a clear circadian rhythm fluctuation [16]. Specifically, the time period of minimum secretion is at 5 am -10 am, and the time period of maximum secretion is at 8 pm - 2 am. Clinical observations showed that acid-related diseases are often associated with sleep disorders. For example, gastroesophageal reflux disease (GERD) is closely related to many types of sleep disorders, such as inadequate sleep, difficulty in falling asleep, sleep disruption, poor sleep quality, and early morning awakening [17]. The results of 24 h esophageal pH monitoring showed that the time period of lowest esophageal pH is in the evening and early morning, and some GERD patients still exhibit nocturnal acid break-through after treatment with a double-dosed proton pump inhibitor (PPI) [18]. In addition, it is found that people with sleep disorders suffer more esophageal acid exposure than normal-sleep people (total acid exposure time: 6.15%±5.89% *vs*. 1.74%±1.54%, $P < 0.05$) [19]. What's more, a survey in South Korean showed that the women with more than 9 h sleep had a lower incidence of peptic ulcer disease (PUD) compared to those with 7 h sleep [20], suggesting a protective effect of adequate sleep on GI mucosa.

### *Statement 6: Sleep-wake rhythm affects the anti-gastroesophageal reflux mechanisms and are correlated with GERD.*

Evidence grade: IIb; Recommendation grade: A; Statement consent rate: 91.9%.

Healthy individuals generally do not develop gastroesophageal reflux during sleep. However, nocturnal acid reflux, insomnia and poor sleep quality are common complaints reported by outpatient visits [17]. In addition to affecting gastric acid secretion, sleep-wake rhythm disturbance may contribute to the development of reflux-related symptoms via affecting the anti-gastroesophageal reflux mechanisms and the intragastric pressure. Eastwood et al. [21] found that the function of lower esophageal sphincter (LES) is not

affected by sleep and posture, and the occurrence of reflux during the wakefulness and sleep is associated with transient LES relaxation (TLESR). TLESR is regulated by the cerebral cortex, with reduced incidence during the deep sleep. TLESR is not seen during the deep sleep at night, and only occurs during the brief awakening or full awakening from sleep [22].

GI motor dysfunction due to low-grade duodenal inflammation is a new therapeutic target for functional dyspepsia (FD), especially for FD combined with GERD and/or IBS [23,24]. Biorhythm dysregulation can affect the coordination of gastric-duodenal movements. The transmission of GI contents relies on the coordinated activity of GI tract, which.is controlled by the circadian clock located at the special stromal cells between the longitudinal and cyclic muscles. The normal slow-wave rhythm of each segment of GI tract is as following: stomach, 3 cycles / min; duodenum, 12 cycles / min; jejunum and ileum, 7 - 10 cycles / min; colon, 12 cycles / min [25]. Disturbance of circadian rhythm resulting from sleep disorders or shift work may disrupt the coordination of esophago-gastric-duodenal movements and lead to GI disorders such as IBS, GERD, and PUD [25].

### *Statement 7: Disorders of sleep-wake and dietary intake rhythms contribute to the pathogenesis of PUD.*

Evidence grade: IIc; Recommendation grade: A; Statement consent rate: 94.6%.

The circadian rhythm of gastric acid secretion matches the feeding rhythm formed during human evolution [26]. The irregular change in daily dietary intake rhythm is one of the etiological factors of PUD. Moreover, recurrent and periodic episodes of epigastric pain are one of the characteristics of FUD. Ulcer pain, displaying obvious rhythm, is correlated with diet behavior. Mental stress and insomnia can induce or aggravate PUD. A research found that some patients with gastric ulcer, especially in those who eat before going to bed, have significantly lower gastric pH values than healthy people ($P < 0.0001$) and could have pain symptoms at night [27].

### *Statement 8: Abnormal biorhythm disrupts GI mucosal barrier, leading to impairment of mucosal defense function.*

Evidence grade: IIc; Recommendation grade: A; Statement consent rate: 97.3%.

Sleep disorders are common in patients with IBD due to the clinical symptoms and disease activity [8, 28-30], which may further promote progression of the disease and affect the patient's quality of life. A recent cross-sectional study among college students found that plasma levels of pro-inflammatory cytokines are significantly higher in individuals with inadequate sleep or late chronotype [31]. The late chronotype is positively correlated with the levels of interleukin-1β (IL-1β), IL-6, tumor necrosis factor-α (TNF-α), and IL-10. Another clinical study also suggested that poor sleep quality is associated with the high risk of surgical treatment and hospitalization in patients with IBD [32]. Moreover, animal studies showed that disruption of circadian rhythm aggravates colonic inflammation and symptoms (diarrhea, abdominal distension and bloody stool) in a mouse model of colitis [33]. Acute and chronic intermittent sleep deprivation both exacerbated colonic inflammation and upregulated the plasma levels of TNF-α, IL-1β, and IL-6 in mice [34]. Circadian rhythm is also involved in the regulation of both innate and adaptive immunity. For example, the proportion of Th17 cells in the small intestine may be affected by the circadian clock. The proportion of Th17 cells in the lamina propria of the small intestinal mucosa of wild-type mice is time-dependent, whereas the proportion lacks such rhythmic changes in $CLOCK^{\Delta 19}$ (circadian clock gene) knockout or mutant mice and in mice maintained in dark conditions [35]. In addition, circadian rhythm disturbance can also increase the permeability of the intestinal mucosa by altering expression of the tight junction protein occludin and thus affects intestinal mucosal barrier function [36].

### *Statement 9: Biorhythm disruption is associated with intestinal flora imbalance.*

Evidence grade: IIc; Recommendation grade: A; Statement consent rate: 97.3%.

The intestinal flora are constantly changing under the influence of biorhythm systems. A research has found that mice with chronic changes of circadian rhythm can develop the imbalance of intestinal flora, with both fecal and jejunal bacterial abundance and biodiversity being reduced [37]. And the imbalance of intestinal flora can further aggravate intestinal mucosal

barrier dysfunction and mucosal inflammation [8]. The metabolites of intestinal flora such as short-chain fatty acids (SCFAs), bile acid metabolites, neuroactive substances, and cytokines released during the immune response can mediate host-microbiome interactions and participate in the regulation of the "gut-brain axis" [38]. It has been shown that circadian fluctuations in SCFAs levels modulate the rhythmic movement of colonic myenteric nerve plexus through the free fatty acid receptor 3 (FFAR3), affecting the colonic contraction movement in mice [39].

*Statement 10: Biorhythm disruption can affect the levels of gut hormones such as gastrin, motilin and cholecystokinin and impair the regular movement of the duodenum, leading to or aggravating bile reflux.*

Evidence grade: III; Recommendation grade: A; Statement consent rate: 100%.

Duodenal inflammation and motor dysregulation are important therapeutic targets for FD symptoms and overlapping FGIDs symptoms [23,40]. Psychological stress as well as rhythm disorders of sleep and dietary are important pathogenic factors of the duodenal inflammation and dysmotility. These factors can cause the changes of levels for peptide hormones such as gastrin, motilin and cholecystokinin. In addition, the abnormal bile acid exposure is both the cause and the consequences of the duodenal motor disorders. Clinically, patients with depression, anxiety and sleep disorders often display symptoms related to bile reflux, which may be associated with the disruption of bile acid metabolic homeostasis [41]. Recent studies have found that mice with circadian rhythm disruption exhibit not only the imbalance of intestinal flora, but also the abnormal expression of hepatic genes involved in the metabolism of bile acid and cholesterol, such as Hmgcr, Soat 2, Abcg 5/8, Cyp7a1 and Cyp2c70, leading to formation of gallstone [42] .

## Diagnosis and evaluation

There is still no international consensus on the diagnosis and evaluation of digestive diseases with biorhythm dysregulation. Based on the clinical experience of digestive psychosomatic experts, the routine examination procedure of FGIDs can be taken as a reference [43,44]. Firstly, the routine examinations are conducted to clarify the existence of organic diseases, and then the gut function and sleep or mental status are evaluated. Sleep disorders are usually manifested as difficulties in falling asleep, sleep fragmentation, early morning awakening, daytime sleepiness, fatigue and so on. The evaluation of sleep disorders helps to quickly identify the patients with biorhythm disorders. Pitsburg Sleep Quality Index (PSQI), Morning and Evening Questionnaire (MEQ), Epworth Sleepiness Scale (ESS), Insomnia Severity Index (ISI) and Sleep Dysfunction Rating Scale (SDRS) can be used.

*Statement 11: Evaluating biorhythm disorders in GERD is beneficial for a more comprehensive understanding of etiology, pathogenesis and treatment of the disease.*

Evidence grade: IIc; Recommendation grade: A; Statement consent rate: 100%.

The pathogenesis of GERD mainly involves abnormal gastric acid secretion and gastroesophageal motility. The latter includes anti-gastroesophageal reflux dysfunction, reduced clearance ability of esophagus, increased intragastric pressure, increased duodenal resistance, bile reflux and so on. Both mechanisms are related to the disturbance of sleep and dietary rhythm [17,19,45]. The evaluation of biorhythm disorders in GERD includes: (1) Sleep disorder evaluation. Sleep disorders and GERD have bi-directional cause-effect relationships. The evaluation tools include PSQI, Hospital Anxiety and Depression Scale (HADS), ISI, ESS, and 8-items Short-Form Health Survey (SF-8). A study on sleep disorders in GERD patients showed that the prevalence of sleep disorders in GERD patients (66/124) is significantly higher than in non-GERD patients (89/226). Depression and anxiety are more common in those with sleep disorders than those without sleep disorders. Daytime sleepiness is more common in GERD patients than in non-GERD patients. The health-related quality of life is worse in those with sleep disorders. The authors suggested that GERD patients with sleep disorders usually experience daytime sleepiness and impaired health-related quality of life [46]. (2) Evaluation of dietary rhythm disorders. Studies have shown that irregular meal pattern, large volume of meals, eating meals just before bedtime are independent risk factors for GERD [45]. (3) Evaluation of depression and anxiety status. As mentioned above, biorhythm disorders often

coexist with depression and anxiety. The evaluation of psychological condition is necessary to identify GERD with biorhythm disorders.

*Statement 12: In the diagnosis and treatment of acid-related disorders, evaluating biorhythm disorders helps to get a comprehensive understanding of disease etiology.*

Evidence grade: IIc; Recommendation grade: A; Statement consent rate: 100%.

Acid-related diseases include mucosal damage caused by gastric acid, acid sensitivity, and abnormal gastric acid secretion. PUD is the most common form of acid-related disease. In addition to the association of gastric acid secretion and circadian rhythm, PUD is accompanied by circadian disturbance manifestations in other systems of the body, such as abnormal sympathetic-adrenal excitation and urinary electrolyte excretion [47,48]. *Helicobmcter plori* (Hp) infection is the main cause of PUD. A study has showed that the circadian rhythmic fluctuations in gastric acid secretion are decreased in Hp-positive individuals [49]. The above findings identify a link between PUD and circadian disturbances. Animal studies have also shown that circadian disturbances and reduced levels of melatonin can weaken the gastric mucosal defense function and are associated with ulcer occurrence [50]. In addition, a study including both healthy people and patients with active duodenal ulcers showed that the circadian rhythm of gastric acid secretion is not associated with plasma gastrin levels, but is regulated by central nervous system-enteric nervous system (CNS-ENS) [51]. Therefore, attention should be paid to the evaluation of biorhythm disorders in the management of PUD. The evaluation of biorhythm disorders in acid-related diseases mainly includes three aspects (identical with those described in statement 11): (1) Sleep disorder evaluation. (2) Dietary rhythm disorder evaluation. (3) Depression and anxiety status evaluation.

*Statement 13: Evaluating biorhythm disorders may be beneficial in the diagnosis and treatment of bile reflux and dyspepsia symptoms.*

Evidence grade: IIa; Recommendation grade: A; Statement consent rate: 97.3%.

Many researches have suggested that duodenal inflammation is a key pathogenesis of FD as well as FD overlapping other upper or lower GI diseases [40,52]. In addition to duodenal dysmotility caused by circadian and dietary rhythm disruption, intraduodenal bile exposure and abnormal metabolites of bile acids are also important factors triggering duodenal inflammation [23]. Animal experiments showed that bile salts and microbes in the intestinal lumen affect each other and jointly trigger inflammation in duodenal mucosa [23]. By gradually changing the circadian rhythm via turning on the lights at a later time, the alterations in microbes of jejunal and fecal samples and metabolites of fecal samples has been detected in rats [37]. A study has shown that disrupted circadian rhythm of eating behavior affects the expression of genes related to the bile acid and cholesterol metabolism as well as the intestinal flora, thus promoting gallstone formation in rats suffering from circadian disturbances and disrupted eating behavior [42]. A clinical study found a trend of increased nighttime exposure to bile acid in esophagus of the GERD patients refractory to PPI treatment compared with the patients sensitive to PPI [53]. Another clinical study showed that the proportion of reflux esophagitis (RE) patients containing bile acids in gastric fluid is significantly higher than healthy controls (85% *vs*. 59%, $P < 0.05$), whose daytime bile acid concentration is 6 to 8 times higher than healthy controls [54]. The authors also found that about 10% of RE patients exhibit pH > 7 values in gastric fluid samples, with the bile acid concentrations > 500 μmol/L. In the RE patients with pH < 4 values in gastric fluid, both bile acids and pepsin coexisted in 98% of these patients. The above findings suggest that bile reflux may be related to circadian disturbances. Therefore, evaluation of circadian rhythm disorders is necessary in the diagnosis and treatment of patients with bile reflux. The methods and tools are as described above.

*Statement 14: Biorhythm disorders are often comorbid with depression and anxiety. Evaluation of psychological status is beneficial for the understanding of the central etiological factors.*

Evidence grade: IIb; Recommendation grade: A; Statement consent rate: 91.9%.

The main manifestations of biorhythm disturbance are circadian and sleep disruption triggered by changes in social and natural environment. Biorhythm

disturbance may yield a profound effect on the body [55]. Circadian rhythm disorders are often comorbid with psychological abnormalities such as depression and anxiety. A study in Netherlands evaluated the sleep duration (SD), sleep efficiency, relative amplitude (RA) of day-time and night-time activity, mid sleep on free days (MSF), gross motor activity (GMA), and moderate-to-vigorous physical activity (MVPA) in 359 subjects [56]. The results showed that the individuals with comorbid depression/anxiety display a significant difference in the objective circadian rhythm and physical activity (PA) compared to controls. And according to self-reported questionnaires, people with depression/anxiety show both shorter and longer SD and more insomnia. The individuals with more severe depression/anxiety show the lowest PA and most circadian rhythm disruption. The CNS-related mechanisms of sleep disorders involve the dysregulation of cortex-network system, autonomic nervous system and hypothalamic-pituitary-adrenal (HPA) axis [57], which occurs in response to the psychological stress. Genetic factors, family history of insomnia, female, and environmental stress are risk factors triggering stress-related sleep disorders. A large cohort study ($n$ = 1,944) in Netherlands showed that depressive and/or anxiety disorders are associated with a late chronotype even when adjusting for sociodemographic, somatic health, and sleep-related factors ($\beta = 0.09$, $P = 0.03$) [58]. Further analysis showed major depressive disorder (MDD) is associated with the late chronotype. Subjects with late chronotype also report more overt diurnal mood variation (worse mood in the morning).

Social rhythmicity refers to the regularity of individuals engaged in social and lifestyle activities, which is of great significance for the prevention and treatment of body diseases, including psychological disorders. Current researches mainly focus on associations between social rhythmicity and bipolar and depression, and sleep may be potentially associated with it. A study including 3,284 adults showed that greater social rhythmicity is directly associated with fewer depressive and anxiety symptoms, and that healthier sleep behaviors and thoughts may mediate this association [59]. Results also highlight the complementary roles for both sleep behaviors and thoughts. The above findings suggest that biorhythm disorders are often combined with psychological stress, depression and anxiety, and cognitive disorders. In the diagnosis of biorhythm disorders, mental status evaluation is necessary.

## Treatment

*Statement 15: Adjusting lifestyle and establishing normal biorhythms (including adequate sleep, regular diet, physical exercise, etc.) can play a role in the prevention and treatment of digestive diseases with biorhythm disruption.*

Evidence grade: IIa; Recommendation grade: A; Statement consent rate: 97.3%.

Biorhythms hav e direct or indirect effects on GI secretion, coordinated movement, intestinal flora, and mucosal defense function. Therefore, maintaining normal sleep, dietary behavior and other rhythms is crucial for the prevention and treatment of digestive diseases [7,8,25,60]. A study in Korea [20] investigated the sleep conditions of 14,290 subjects (8,209 women) between 2008 and 2009 using multiple Logistic regression models to evaluate the relationship between PUD and sleep duration. The results showed that the prevalence of PUD in the population is 5.7%, and it is higher in men than in women (6.8% *vs*. 4.9%). Furthermore, the prevalence of PUD in women with 9 h sleep duration is significantly lower than in women with 7 h sleep duration. What's more, eating time and rhythm are also important factors related to the occurrence and severity of digestive diseases [26]. Eating time and food types should be coordinated with the human daily rhythm. Time-restricted eating, that is, eating at regular times every day, may reduce body mass, improve insulin sensitivity, reduce oxidative stress, and reduce blood pressure. In addition, regular exercise can enhance the energy metabolism of carbohydrates, fatty acids, ketone bodies and amino acids, which can also produce beneficial effects on digestive diseases [60]. Regular and moderate exercise can relieve the symptoms of digestive diseases such as RE, PUD, cholelithiasis, constipation, and IBD [61], and help to the recovery of organic diseases. Moreover, regular exercise can also reduce the risk of colon cancer occurrence and recurrence [62]. However, extensive evidence has suggested that high-intensity or

long endurance exercise can exacerbate GI symptoms [61]. In summary, normal biorhythms (including adequate sleep, regular diet, physical exercise, etc.) seems to crucial for the prevention and treatment of digestive system diseases.

### *Statement 16: Melatonin and melatonin receptor agonists can be used for the treatment of digestive diseases with biorhythm disuption and/or depression and anxiety.*

Evidence grade: I; Recommendation grade: A; Statement consent rate: 100%.

Melatonin (N-acetyl-5-methoxytryptamine) is mainly produced by the pineal gland at night under normal circadian rhythm, and then enters the blood circulation to stabilize and strengthen the circadian rhythm through the melatonin receptors [63]. Melatonin receptors are present in the human brain, retina, liver, kidney, GI tract, skin, and immune cells. The targets of melatonin and melatonin receptor agonists include CNS, peripheral system related to gut-brain interactionS, and CNS-ENS interactions. A Meta-analysis containing 19 randomized, placebo-controlled trials showed that melatonin is effective in reducing sleep latency (weighted mean difference (WMD) = 7.06 minutes (95% CI: 4.37 - 9.75), Z = 5.15, $P < 0.001$) and increasing total sleep time (WMD = 8.25 minutes (95% CI: 1.74 - 14.75), Z = 2.48, $P < 0.013$). What's more, the overall sleep quality significantly improves in subjects taking melatonin (standardized mean difference = 0.22 (95% CI: 0.12 - 0.32), Z = 4.52, $P < 0.001$) compared to placebo [64]. However, melatonin has a first-pass effect, which is mostly metabolized by the liver after oral administration, and has a short half-life (about 40 min) and maintenance time [65]. Compared with melatonin, its receptor agonist has a long half-life (1 - 2 h), and its affinity for melatonin receptors is greater than that for melatonin [66]. Therefore, melatonin receptor (MT1, MT2) agonists are currently used in the treatment of sleep disorders, which include agomelatine, ramelteon and tasimelteon [66-69].

Basic studies have shown the presence of melatonin and its synthetase in the GI tract, indicating that melatonin can be synthesized in the gut [70]. Studies of the distribution and role of melatonin receptors in the GI tract by using radiolabeled 2-$^{125}$I-melatonin showed that melatonin receptors exist in the GI tract of duck, chicken and human, and the binding to ligands is fast, stable, reversible, and specific with high affinity. In the duck GI tract, the density order of 2-$^{125}$I-melatonin binding site is ileum/jejunum > duodenum/colon > cecum > esophagus, with the highest density in the mucosa of small intestinal, cecum and colon. In cells, the density order of binding sites is nucleus > microsome > mitochondria >> cytoplasm. These findings are consistent with the role of melatonin in the GI tract. It can be speculated that melatonin receptor agonists may be used in the treatment of digestive diseases.

It has been also found that melatonin exerts both anti-oxidant and anti-inflammatory effects. In a study using a mouse colitis model, in which mice received melatonin at 4 mg/kg orally or two melatonin receptor agonists twice daily for 3 days, melatonin alone can significantly reduce gross and histological damage scores and inhibit the activity of myeloperoxidase (MPO), while neither of the melatonin receptor agonists alleviated colonic inflammation, indicating a direct effect of melatonin in the gut [71].

According to the above findings, the potential indications of melatonin or melatonin receptor agonists are: (1) Digestive diseases with sleep problems associated with circadian rhythm disruption. (2) Dysfunction of rhythmic coordination in the GI tract. (3) Digestive diseases with depression and anxiety.

### *Statement 17: Melatonin or melatonin receptor agonists can be used as complementary agents for the treatment of GERD with biorhythm disorders.*

Evidence grade: IIa; Recommendation grade: B; Statement consent rate: 91.9%.

Circadian rhythm disorders participate in the pathogenesis of GERD through various mechanisms such as gastric acid secretion, anti-reflux function, esophagogastric-duodenal coordinated movement, and mucosal defense function. Melatonin produced in the GI tract has a mucosal protective effect. It can also inhibit gastric acid secretion while promote gastrin release, leading to enhanced contraction of LES [72]. Therefore, melatonin or melatonin receptor agonists are suitable for treating GERD patients with

biorhythm disorders. Previous studies have suggested that melatonin and its receptor agonists can improve the symptoms of sleep disturbances or depression and anxiety in patients with GERD, and enhance the esophageal mucosal defense function [73-75]. In addition, animal studies have confirmed that melatonin could prevent esophageal injury, increase esophageal mucosal blood flow and the level of prostaglandin E2 (PGE2) in mucosa, while reducing TNF-α levels [76]. Another study observing the therapeutic effect of melatonin on acid reflux-related esophageal mucosal injury showed that melatonin could play a protective effect on acid reflux-induced damage by stimulating MT2 receptors, leading to the release of nitric oxide (NO) and calcitonin gene-related peptide (CGRP) from sensory nerves, while inhibiting the expression and release of TNF-α and IL-1β [77].

Furthermore, a clinical trial showed that GERD patients treated with omeprazole and melatonin had reduced basal acid output (BAO) ((15.8 ± 0.9) mmol/h *vs* (17.2 ± 0.7) mmol/h, $P = 0.09$), and increased LES pressure ((14.5 ± 1.3) mmHg *vs*. (10.4 ± 4.0) mmHg, $P = 0.002$), and the combination can improve the therapeutic effect of omeprazole and shorten the treatment time [78]. Another small sample ($n = 16$) study showed that GERD patients with insomnia obtained significantly improved reflux symptoms and sleep disturbances after the treatment of ramelteon [79]. Compared with placebo, there was a significant improvement ( $P < 0.05$) in daytime heartburn (-42% *vs*. -29%), night heartburn (-42% *vs*. 78%), heartburn during 24 h (-42% *vs*. -3%) and acid reflux during 24 h (-26% *vs*. 19%), along with a significant decrease in the ISI score (-46% *vs*. -5%, $P < 0.05$).

In addition, a review discussed the role of melatonin in the long-term protective effect of GERD, Barrett's esophagus and esophageal adenocarcinoma based on the short-term protective effect of melatonin on acute RE [80]. It provided the evidence that melatonin may play a protective role against esophageal erosion, Barrett esophagus and even esophageal tumor in various animal models and clinical patients with GERD.

Based on the above findings, the potential indications of melatonin or melatonin receptor agonists for GERD include: (1) GERD with sleep problems related to biorhythm disorders. (2) GERD with clinical manifestations of depression and anxiety. (3) Refractory esophagogastric-duodenal motor dysfunction.

*Statement 18: Melatonin or melatonin receptor agonists can be tried to treat peptic ulcer diseases with biorhythm disruption.*

Evidence grade: III; Recommendation grade: B; Statement consent rate: 97.3%.

Melatonin and its receptor agonists can reduce acid and bile reflux to treat PUD by regulating gastric acid secretion, alleviating inflammatory response, enhancing mucosal defense and repair ability, and coordinating GI motility [81]. In addition, they can also prevent PUD through improving sleep, depression and anxiety states. A Study in an acetic acid-induced rat gastric ulcer model has found that except from affecting the cyclooxygenase-2 (COX-2) - PG system to promote PG production, activating the constitutive nitric oxide synthase (cNOS) - NO system and stimulating the expression of CGRP in sensory nerves, melatonin and its precursor L-tryptophan can promote mucosal cell proliferation and mucosal repair through the release of gastrin and ghrelin, thus accelerating the ulcer healing. In an animal model of gastric ulcer induced by indometacin, agomelatine reduces the levels of pro-inflammatory cytokines (TNF-α, IL-1β and IL-6) and alleviates oxidative stress in the gastric mucosa, accelerating gastric mucosal healing [82]. Its efficacy is similar to omeprazole [83].

In conclusion, the current results of basic and clinical studies suggest that in the treatment of PUD, melatonin and its receptor agonists can accelerate ulcer healing, and may be a kind of complementary medicine. The indications for applying these drugs include biorhythm-associated sleep disorders, depression and anxiety, accelerating mucosal repair, reducing inflammation, regulating gastric acid and pepsin secretion, and non-steroidal anti-inflammatory drugs (NSAIDs) -related mucosal injury.

*Statement 19: Melatonin or melatonin receptor agonists can be tried as a complementary treatment for FGIDs to improve sleep disorders, depression and anxiety states and coordination of gut function.*

Evidence grade: I; Recommendation grade: A;

Statement consent rate: 91.9%.

Several studies have applied melatonin or melatonin receptor agonists for the treatment of IBS and FD [84-87]. A randomized controlled trial in China has evaluated whether melatonin can effectively improve GI symptoms in IBS patients with sleep disorders. A total of 40 patients randomized to receive melatonin (3 mg) or placebo for 2 weeks. The results showed that melatonin significantly reduces the scores of abdominal pain (2.35 *vs*. 0.70, $P < 0.001$) and increases the threshold of rectal pain (8.9 mmHg *vs*. 1.2 mmHg, $P < 0.01$) compared with placebo [85]. Another study observed the clinical efficacy of agomelatine combined with trimebutine on IBS, showing that the total response rate of GI symptoms is significantly higher in the combination therapy group than the monotherapy (trimebutine) group (93.7% *vs*. 68.7%, $P < 0.05$) [86]. In addition, the scores of depression, anxiety and sleep status are improved after 1 week of treatment, and the improvement was more obvious over time, with significantly better than the monotherapy group ($P < 0.05$). A study also found that agomelatine (25 mg/d) combined with low-dose olanzapine (1.7 mg/d) improves dyspepsia symptoms, depression, anxiety, and sleep disturbance in patients with postprandial discomfort syndrome (a subtype of FD) [87]. After 8-week treatment, the total response rate is significantly higher than in the group treated with flupentixol and melitracen tablets (94.9% *vs*. 84.9%, $P = 0.026$). And the incidence of adverse reactions is significantly lower than that in the control group, including constipation (2.0% *vs*. 9.3%, $P = 0.047$) and somnolence (1.0% *vs*. 8.1%, $P = 0.027$).

### *Statement 20: Melatonin or melatonin receptor agonists can be tried to treat gut mucosal inflammation-related diseases with biorhythm disruption.*

Evidence grade: III; Recommendation grade: C; Statement consent rate: 81.1%.

A study has found that melatonin attenuates colitis in sleep deprived mice. The intestinal mucosal damage and gut flora imbalance caused by sleep-deprivation is closely related to suppression of melatonin secretion. As an antioxidant, melatonin can reverse the intestinal barrier dysfunction and mucosal damage induced by sleep-deprivation by inhibiting oxidative stress and nuclear factor-kB (NF-kB) signaling pathway [88-90]. What's more, the results of studies using melatonin for sleep disorders in IBD patients have revealed a correlation between the inflammation progression and circadian disturbance [91,92]. Free radicals accumulation, apoptosis, and inflammatory damage in patients with ulcerative colitis (UC) and Crohn's disease (CD) is associated with reduced melatonin levels [93]. Therefore, randomized controlled trials with a large sample are necessary to clarify the clinical efficacy of melatonin and its receptor agonists on IBD patients so that it can be used more reasonably and safely in the prevention and treatment of IBD.

### *Statement 21: Melatonin or melatonin receptor agonists can be tried to attenuate intestinal flora imbalance with biorhythm disruption.*

Evidence grade: III; Recommendation grade: C; Statement consent rate: 83.8%.

Melatonin affects the intestinal flora through multiple mechanisms, including affecting the metabolism of lipids and other nutrients, and affecting the neuroimmune function. Studies have found that sleep deficiency enhances the susceptibility to infection, increases food intake, reduces physical activity, and activates the HPA axis, thus affecting the distribution of the intestinal flora. The latter in turn influences sleep by regulating intestinal neurotransmitters or immune pathways [94,95].An animal study found that both microbiota transplantation from melatonin-treated mice and sodium acetate treatment alleviate high-fat diet-induced lipid metabolic disorders [96]. It has been shown that SCFAs levels are decreased in high-fat diet-fed mice, while melatonin treatment improves the production of acetic acid via enhancing the abundance of Bacteroides and Alistipes. These results suggest that melatonin improves lipid metabolism in high-fat diet-fed mice, and the mechanisms may be associated with the reconstruction of gut microbiota. Another study found that oral melatonin decreases the quantity of *E.coli*-generated lipopolysaccharide (LPS) to ameliorate lipid metabolism abnormality in ileum and epididymal white adipose tissues. Compared with the control mice, jet-lag mice had a higher level of ileal lipid uptake, fat accumulation in ileum and epididymal white adipose tissues, and a lower level of

circulating angiopoietin-like 4 (ANGPTL4) [97]. Jet-lag mice also show a significantly higher abundance of *E. coli* and LPS than the control mice. Conversely, oral melatonin supplementation remarkably reversed the above effects. The test of depletion of gut microbiota further demonstrated that oral melatonin-mediated improvement on lipometabolism in jet-lag mice are dependent on the presence of gut microbiota. The above findings suggest that the intestinal flora and its metabolites may be potential therapeutic targets to ameliorate the lipid metabolism disorders associated with circadian rhythm disruption.

## Conclusion

This consensus adds biorhythm factors into the evaluation of digestive diseases, which may help gastroenterologist to improve the awareness of biorhythm disorders, identify the potential risk factors, better understand the pathogenesis of digestive diseases, and explore new therapeutic targets. For patients with digestive diseases combined with biorhythm disruption, it is a new therapeutic direction to reconstruct normal biorhythm and obtain more benefit for patients. It is expected that more large-scale and high-quality studies can be conducted in the future to provide more favorable evidence and improve the consensus opinion on the clinical management of digestive diseases combined with biorhythm disruption.

## Conflicts of interest statement

None declared.

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