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ROLE OF PROKINETIC AGENTS IN PREVENTING SMALL INTESTINAL BACTERIAL OVERGROWTH (SIBO) RECURRENCE: A NARRATIVE REVIEW

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ABSTRACT

Background: Small intestinal bacterial overgrowth (SIBO) involves the pathological proliferation of bacteria in the small bowel, causing symptoms like bloating and abdominal pain. Although rifaximin is effective for initial eradication, the condition frequently relapses. This recurrence is primarily driven by the failure of the migrating motor complex (MMC), specifically its phase III "housekeeping" function.
Aim: This review evaluates the clinical utility of prokinetic agents in maintaining SIBO remission and examines whether their administration extends the symptom-free interval in high-risk populations.
Material and methods: A systematic search of PubMed and Scopus was conducted to synthesize evidence on MMC dysfunction and the efficacy of various prokinetic agents in preventing bacterial regrowth.
Results: Research indicates that SIBO patients experience a 60% reduction in MMC-related clearance compared to healthy controls. The synergistic integration of prokinetic therapy into the antibiotic eradication phase has been shown to significantly enhance bacterial clearance rates. Among these agents, prucalopride demonstrates high efficacy in delaying relapses and extending the duration of remission. Clinical success depends heavily on nocturnal dosing during the interdigestive state to maximize mechanical cleansing.
Conclusions: Prokinetic pharmacotherapy is an essential component of maintaining remission in SIBO by directly addressing MMC dysfunction - the primary pathophysiological cause of relapse. The selection of a therapeutic agent should be tailored to the patient's clinical phenotype, considering metabolic safety and the symptom profile. Despite promising data, this review underscores the need for large-scale randomized controlled trials to establish standardized diagnostic and therapeutic guidelines.

KEYWORDS

Small Intestinal Bacterial Overgrowth; SIBO; Prokinetic Agents; Migrating Motor Complex; MMC; Gastrointestinal Motility

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Introduction

Small intestinal bacterial overgrowth (SIBO) is an abnormal increase in the number of bacteria in the small intestine. This causes various nonspecific gastrointestinal symptoms (Pimentel et al. 2020). The pathophysiology involves colonization of the proximal small intestine by bacteria, such as *Escherichia coli* and *Shigella*, which are usually found in the large intestine. These bacteria can cause digestive and absorptive disorders (Pimentel et al. 2020; Bushyhead and Quigley 2022).

The diagnosis of SIBO involves both direct and indirect methods. Some experts consider culture-based quantitative and qualitative analysis of proximal jejunum or duodenal samples to be the gold standard. The diagnosis is confirmed by the presence of $\geq 10^3$ CFU/mL (colony-forming units per milliliter) in the aspirate (Pimentel et al. 2020). Due to the invasive nature and procedural complexity of aspirate analysis, non-invasive breath tests (BT), utilizing either glucose or lactulose, have become the preferred diagnostic modality in clinical practice (Silva et al. 2025). A diagnostic result is defined as an increase in the hydrogen concentration of ≥ 20 ppm relative to the baseline value within 90–120 min. However, diagnostic accuracy remains a concern for both hydrogen and hydrogen-methane breath tests. Specifically, the sensitivity of the glucose (GBT) and lactulose (LBT) variants is estimated at 30–68% and

20–93%, respectively. Due to these limitations, a negative result is insufficient to rule out SIBO (Pimentel et al. 2020). Diagnostic challenges arise from inter-individual variability in intestinal transit time among patients and the lack of complete standardization of test preparation (Silva et al. 2025).

The clinical symptoms of SIBO include bloating, flatulence, abdominal pain, and chronic diarrhea. Weight loss, anemia, fat-soluble vitamin deficiencies, and mucosal inflammation of the small intestine may occur in severe or protracted cases (Pimentel et al. 2020). The differential diagnosis is complicated by the high rate of comorbidity between SIBO and irritable bowel syndrome (IBS) as well as other disorders of gut-brain interaction (DGBI) (von Muhlenbrock et al. 2025). Meta-analyses have suggested that SIBO affects as many as 78% of patients with IBS (Pimentel et al. 2020). The overlap of symptoms indicates that a multifaceted clinical approach is often required before a definitive diagnosis can be made.

Antibiotic therapy remains the cornerstone of treatment, with rifaximin, a minimally absorbed broad-spectrum antibiotic, playing a central role (Silva et al. 2025). Meta-analyses confirm its safety and efficacy, showing significant symptom improvement and normalization of breath test results (Gatta et al. 2017; Takakura et al. 2024). Accordingly, the American College of Gastroenterology recommends a dose of 550 mg three times daily for 14 days (Pimentel et al. 2020).

While initial eradication is often successful, SIBO recurrence rates remain high (Lauritano et al. 2008). Predisposing factors range from patient-specific variables such as advanced age and prior appendectomy. Additionally, chronic use of proton pump inhibitors (PPIs) contributes to this risk by disrupting the gastric acid barrier (Lo and Chan 2013). Recurrence is primarily driven by the impairment of intestinal cleansing mechanisms. Specifically, disruption of phase III of the migrating motor complex (MMC) prevents the clearance of bacteria and debris toward the colon. This mechanism serves as a primary defense against overgrowth (Bushyhead and Quigley 2022). Although previous guidelines noted insufficient evidence for the routine use of prokinetics (Pimentel et al. 2020), recent data from a network meta-analysis (NMA) suggest that prokinetics are an effective component of therapy, particularly in patients with functional gastrointestinal disorders (Usai-Satta et al. 2022; Zhang et al. 2025).

The present review aims to evaluate the role of prokinetic agents in preventing SIBO recurrence. It examines the mechanisms underlying gastrointestinal motility stimulation to maintain remission and seeks to answer the following clinical question: Does routine use of prokinetic agents after rifaximin eradication significantly prolong the symptom-free period in high-risk patients?

Methodology

A systematic literature search was conducted using PubMed, BioMed Central, Scopus, and Google Scholar to identify relevant studies on the role of prokinetic agents in preventing SIBO recurrence. The search strategy utilized keywords and their combinations, including *Small Intestinal Bacterial Overgrowth, SIBO, prokinetics, Migrating Motor Complex, MMC,* and *recurrence prevention*. Additionally, reference lists of eligible articles were manually searched to identify additional relevant studies. The analysis encompassed

meta-analyses as well as prospective and randomized controlled trials published through April 2026. Based on the available literature, data were synthesized to evaluate the efficacy of different pharmacological classes and herbal interventions in preventing bacterial overgrowth recurrence.

Results

1. Pathophysiology and Rationale for Prokinetics Use

1.1 SIBO recurrence rates: a clinical perspective

A significant clinical challenge is the high rate of SIBO recurrence, which underlies the chronic and relapsing character of the disorder. Antibiotic therapy alone rarely results in sustained remission. A prospective evaluation of patients following successful rifaximin eradication (confirmed by a negative breath test) revealed a progressive increase in relapses: 2.6% at 3 months, 27.5% by 6 months, and as high as 43.7% following 9 months (Lauritano et al. 2008). These observations are consistent with the time-to-symptom return analyses. The median time to symptom recurrence in patients who did not receive maintenance therapy was only 59.7 ± 47.4 days (Pimentel et al. 2009). Such a short remission period justifies the use of prokinetics as a "motility aid" that supports intestinal transit and consolidates the eradication effect.

1.2 Pathophysiological Basis of Relapses: Dysfunction of the Migrating Motor Complex (MMC)

The key defense mechanism of the small intestine that prevents SIBO is the Migrating Motor Complex (MMC), often termed the "physiological housekeeper" (Deloose and Tack 2016). This is an intense, phasic, and tonic contractile phenomenon that begins in the proximal part of the intestine and moves toward the colon. It transports undigested debris, including desquamated epithelium and excess bacteria from the small to large intestine (Pimentel et al. 2020).

MMC consists of four phases with distinct characteristics:

- Phase I: Motor rest phase (45–60 min); absence of contractile activity generating a wave (Deloose et al. 2012).
- Phase II: A period of irregular, low-amplitude activity (30–45 min), during which the contraction frequency gradually increases (Deloose et al. 2012).
- Phase III (Activity Front): A series of rhythmic, intense contractions at maximum frequency (approximately 3 contractions/min in the stomach and 11–12 contractions/min in the duodenum), lasting for 5–10 min (Deloose and Tack 2016). The propagation of the wave from the stomach to the distal ileum ensures mechanical cleansing of the intestinal lumen and is a key element in SIBO prevention (Deloose et al. 2012).
- Phase IV: A short transitional period (up to 5 min) before the start of the next cycle (Deloose et al. 2012).

MMC regulation is based on neurohormonal signal integration. The main regulator of phase III of gastric origin is motilin, released cyclically by Mo cells in the duodenum (Deloose and Tack 2016). Peak motilin concentration is closely correlated with the onset of phase III in the

pre-pyloric portion of the stomach. Ghrelin and serotonin also play significant roles; serotonin is responsible for initiating contractions in the small intestine via 5-HT_4 receptors. In contrast to the stomach, whose contractile activity is stimulated by the vagus nerve, the distal segments of the gastrointestinal tract are autonomously controlled by the enteric nervous system (ENS), which spontaneously generates their activity (Deloose et al. 2012).

1.3 Clinical significance of MMC dysfunction in SIBO

Manometric studies have confirmed the association between MMC dysfunction and small intestine bacterial colonization. Phase III is often absent or its progression is significantly impaired in patients with SIBO. Analyses have shown that individuals with SIBO and IBS generate only 0.7 ± 0.8 phase III episodes over 4 hours (compared to 2.2 ± 1.0 in healthy individuals). The duration of phase III itself was also shortened from 5.3 to 3.1 minutes. This represents a reduction of over 60% in the cleansing activity (Pimentel et al. 2002). This impairment creates a self-perpetuating cycle. The initial impairment of MMC promotes colonization by gas-producing microorganisms, such as methanogens, which slows intestinal transit by nearly 59%. Bacterial metabolic products can cause secondary damage to the ENS, which in turn inhibits gastrointestinal motility and hinders bacterial eradication (Pimentel et al. 2006).

1.4 Clinical Mechanisms of Motility Impairment

SIBO relapses have multiple underlying causes. One of these factors is age. It has been demonstrated that as the body ages, the frequency and amplitude of phase III of the MMC decrease (Lauritano et al. 2008; Deloose et al. 2012). Systemic diseases are also key contributors. Fibrosis of the smooth muscle in systemic sclerosis leads to nearly complete loss of gastrointestinal motility (Deloose et al. 2012). In contrast, damage to the nerves of the autonomic nervous system (autonomic neuropathy) occurs in patients with diabetes, Parkinson's disease, or hypothyroidism, resulting in less frequent MMC cycles and food retention. Digestive disorders associated with conditions such as chronic pancreatitis and cystic fibrosis are significant risk factors. The presence of undigested food residues in the small intestine lumen serves as a direct metabolic substrate for bacteria, promoting their excessive proliferation. Anatomical abnormalities, such as postoperative adhesions, intestinal strictures following radiation therapy, or bariatric bypass procedures, constitute a key barrier that disrupts the MMC wave continuity (Bures et al. 2010). Resection of the ileocecal valve (ICV), which limits the backflow of anaerobic bacteria from the large intestine to the small intestine, is a critical factor (Bushyhead and Quigley 2022). Pharmacotherapy, particularly long-term use of proton pump inhibitors (PPIs), increases the risk of SIBO recurrence (OR 3.52; 95% CI 1.07–11.64) (Lauritano et al. 2008). Pathophysiologically, PPIs increase the pH of gastric juice by inhibiting the H^+/K^+-ATPase pump activity, leading to hypochlorhydria. This allows pathogens that would otherwise be immediately neutralized in a normal, highly acidic environment to survive (Lo and Chan 2013). Excessive bacterial colonization of the upper small intestine is found in over 50% of patients taking omeprazole (Lauritano et al. 2008). The autoimmune etiology of post-infectious SIBO is a significant clinical phenomenon that is initiated by exposure to the bacterial toxin CdtB. It induces the production of anti-CdtB antibodies, which attack vinculin via molecular mimicry. This process leads to damage to this protein within Interstitial Cells of Cajal (ICC), which act as pacemakers for gastrointestinal motility, and to the loss of the body's ability to initiate phase III of the MMC (Pimentel et al. 2015).

1.5 Limitations of Alternative Strategies and the Role of Prokinetics

Although a low-FODMAP diet effectively alleviates gastrointestinal symptoms, it does not address the underlying cause of the condition, which is MMC dysfunction. According to the latest information, the low-FODMAP diet likely contributes to changes in the bacterial composition of the gastrointestinal tract, including *Bifidobacterium* and *Faecalibacterium prausnitzii*, which appears significant given the challenges of treating individuals with SIBO (Staudacher and Whelan 2017). Probiotics are not routinely recommended by the ACG due to a lack of strong evidence for their efficacy (Pimentel et al. 2020). Moreover, administering probiotics to SIBO patients can lead to the intensification of bloating, metabolic lactic acidosis, and neurocognitive impairment, often described as "brain fog" (cognitive impairment) (Rao et al. 2018). These symptoms resolved after discontinuing probiotic therapy and initiating antibiotic treatment (Deloose et al. 2012). Despite its widespread use, cyclic antibiotic therapy has limitations and shortcomings. It often eliminates symptoms only temporarily and carries the risk of developing drug resistance, particularly when systemic antibiotics are used. It does not restore the small intestine's physiological mechanical clearance, which often leads to recurrence after therapy discontinuation (Pimentel et al. 2009; Rezaie et al. 2016). In this context, prokinetic therapy addresses the underlying pathophysiology by inducing an exogenous phase III of the MMC. This process breaks the vicious cycle and is the main component of relapse prevention (Pimentel et al. 2009). The following section provides an overview of the prokinetic agents used for SIBO treatment.

2. Overview of Individual Prokinetics

Prokinetics are medicines that affect complex neurohormonal mechanisms. These agents promote gastrointestinal motility by stimulating smooth muscle contractions and enhancing esophageal peristalsis. Furthermore, they accelerate gastric emptying while shortening total intestinal transit time. The activity of these medications is based on the modulation of three key receptors: serotonin, motilin, and dopamine receptors. In the digestive system, the primary neurotransmitter is acetylcholine (ACh). Serotonin stimulates the release of ACh from cholinergic nerve endings via 5-HT_4 receptors, increasing the contractile activity of the gastrointestinal tract. Subsequently, dopamine primarily exerts an inhibitory effect on motility by acting via D_2 receptors and inhibiting ACh release. The three main groups of currently used prokinetics are dopamine D_2 receptor antagonists, serotonin 5-HT_4 receptor agonists, and motilin receptor agonists (Mulak 2014).

2.1 Prucalopride

Prucalopride is a selective agonist with high affinity for 5-HT_4 serotonin receptors. It is currently among the most extensively studied new-generation prokinetics (Quigley 2017). Unlike earlier-generation agents such as cisapride, it is characterized by high selectivity for 5-HT_4 receptors, which reduces the risk of interactions with extraintestinal serotonin receptor subtypes and hERG potassium channels (Tack et al. 2012; Mendzelevski et al. 2012). The mechanism of action of prucalopride appears to be more complex than that of classical neurostimulation. 5-HT_4 receptor expression has been directly demonstrated in small intestinal epithelial cells (enterocytes). Stimulation of these receptors directly from the gastrointestinal tract lumen is sufficient to trigger the peristaltic reflex, which is critical for preventing bacterial stasis (Konen et al. 2021).

Scintigraphic studies and high-resolution manometry (HRM) confirm that prucalopride reduces the gastric half-emptying time for solids from 71 min (placebo) to 54 min ($p < 0.001$). Furthermore, it reduced the total time of acid exposure in the esophagus from 4.0% (placebo) to 2.4% ($p = 0.02$). This suggests efficacy in distal segments as well as potential utility in treating gastroesophageal reflux disease (GERD) (Kessing et al. 2014).

A unique feature of prucalopride is its neuroprotective and regenerative effects within the enteric nervous system (ENS). This molecule protects Auerbach's plexus neurons by preventing apoptosis induced by oxidative stress. Such stress is frequently associated with chronic inflammation and dysbiosis. This mechanism inhibits the organized proteolytic process (the caspase cascade). In particular, caspase-3 and caspase-7 are suppressed. In addition, as demonstrated in experimental studies, long-term 5-HT_4 receptor activation drives neurogenesis via CREB-dependent pathways. This feature may be crucial in patients whose SIBO etiology is associated with post-infectious damage to ENS neurons. Prucalopride's ability to regenerate the structures responsible for generating peristaltic cycles offers significant potential for restoring physiological intestinal clearance (Bianco et al. 2016; Liu et al. 2009).

The clinical efficacy of 5-HT_4 agonists in SIBO prevention is supported by data showing an extended remission period following antibiotic eradication. Among evaluated agents, tegaserod provided the longest duration of remission, with a mean of 241. 6 symptom-free days for patients with both IBS and SIBO. It was

demonstrated that this medicine statistically delayed the return of symptoms compared to the group of patients without prophylaxis, in whom symptoms recurred on average after 59.7 days ($P = 0.003$). Switching to tegaserod nearly doubled the time to the next relapse from 105.8 to 199.7 days in patients who experienced a relapse while taking erythromycin (Pimentel et al. 2009). Although the original analyses focused on tegaserod, the current clinical practice favors prucalopride, as it offers a superior safety and tolerability profile.

The standard therapeutic dose of 2 mg once daily is optimal for most adults. Studies have shown that starting treatment with a 1 mg dose is safer, particularly in people aged > 65 years (Camilleri et al. 2016; T. Yang et al. 2021). Due to the medication's long half-life of approximately 24 hours, once-daily administration is sufficient to maintain a consistent prokinetic effect (Camilleri et al. 2016). To prevent recurrence, low-dose 5-HT_4 agonists should be administered at bedtime to specifically stimulate phase III of the MMC (Pimentel et al. 2009).

Prucalopride effectively alleviates subjective dyspeptic symptoms, including bloating and postprandial fullness, alongside abdominal pain, which often persist after antibiotic therapy. Clinical studies show that in patients with gastroparesis, this medication significantly reduces symptoms assessed on the GCSI (Gastroparesis Cardinal Symptom Index) scale, which translates into a marked improvement in patients' quality of life (Camilleri et al. 2016; Carbone et al. 2019).

Prucalopride has a high cardiovascular safety profile. It exhibits more than 150-fold greater 5-HT_4 receptor selectivity than older-generation agents, such as cisapride. Clinical studies, including thorough QT studies, have shown that both therapeutic doses (2 mg) and supratherapeutic doses (up to 10 mg) do not cause clinically significant prolongation of the QTc interval. Consequently, the medication does not bind to hERG potassium channels and does not increase the risk of life-threatening ventricular arrhythmias, such as *torsades de pointes* (Mendzelevski et al. 2012; Tack et al. 2012). Most adverse effects following prucalopride use are described as mild or moderate. The most common symptoms include headaches along with gastrointestinal complaints like nausea and diarrhea (Camilleri et al. 2016).

2.2 Erythromycin

Erythromycin belongs to the macrolide class and was originally isolated from the bacterium *Saccharopolyspora erythraea* in the 1950s (Hawkyard and Koerner 2007). In addition to its classic antibacterial action, it functions as a prokinetic agent, acting as a direct motilin receptor agonist. The structural similarity of erythromycin to the natural hormone motilin allows it to bind to receptors in the gastrointestinal tract smooth muscles and nerves. This agent induces an exogenous phase III of the MMC, mimicking physiological motility patterns (Pimentel et al. 2009). The resulting contractions exhibit high amplitudes, often exceeding 100 mmHg. They originate in the antral portion of the stomach and distally propagate along the entire small intestine. Erythromycin prevents the stasis of gastric contents and bacterial recolonization (Nasr et al. 2009).

Nocturnal administration of low-dose erythromycin (50 mg) has been shown to significantly delay symptom recurrence in patients following successful SIBO eradication. Analysis of the results from the primary study group of 42 patients showed that the mean remission duration was 138.5 days. When all treatment cycles were included, this duration increased to 146 days, representing a significant improvement compared to the control group not receiving prokinetics. The mean time to recurrence in the control group (no prophylaxis) was 59.7 days (in the primary analysis, n = 6) and 50.4 days (in the pooled analysis, n = 9). The difference was statistically significant ($p = 0.05$). These results indicate that the nocturnal stimulation of phase III MMC is a key element in sustaining the eradication effect (Pimentel et al. 2009).

Despite the high efficacy of erythromycin, its main limitation is tachyphylaxis, or a diminished pharmacological response following chronic stimulation. This phenomenon results from the down-regulation of motilin receptors. Consequently, the agent ceases to induce phase III MMC after a certain period. In clinical practice, this reduces the use of erythromycin for long-term treatments (Usai-Satta et al. 2022; Deloose and Tack 2016).

An additional risk is posed by numerous pharmacokinetic interactions resulting from strong inhibition of cytochrome P450, particularly the CYP3A4 isoenzyme. This leads to impaired metabolism of many other substances, resulting in elevated concentrations in the body and increasing the risk of toxicity. Concomitant administration of erythromycin with statins carries a risk of rhabdomyolysis; it increases the risk of bleeding with warfarin, and may lead to severe hypotension with calcium channel blockers (Deeraksa 2024). Furthermore, the literature emphasizes that the use of erythromycin as a prokinetic agent raises concerns about the development of bacterial resistance to macrolide antibiotics (Hawkyard and Koerner 2007).

A favorable pharmacological alternative is azithromycin, a newer-generation macrolide antibiotic. Studies show equivalent efficacy in accelerating gastric emptying in patients with gastroparesis. The advantage of this compound is the lack of cytochrome P450 isoenzyme inhibition, which helps avoid clinically significant medication interactions characteristic of erythromycin. As a result, azithromycin has a high safety profile and a lower risk of QT prolongation. The medication is better tolerated by patients and is less likely to cause adverse effects, such as nausea and vomiting. An additional advantage is its long half-life of approximately 68 hours, which allows for once-daily administration (Larson et al. 2010).

2.3 Low-dose naltrexone (LDN)

Naltrexone is a long-acting, specific opioid receptor antagonist used to treat alcohol and opioid dependence at doses of 50–100 mg per day. In recent years, low-dose naltrexone therapy has gained increasing popularity; it involves the use of doses 10 times lower (1–4.5 mg) than those approved by the Food and Drug Administration (FDA) or the European Medicines Agency (EMA) (Younger et al. 2014). Currently, LDN is being investigated for its potential efficacy across a broad spectrum of conditions, including neurodegenerative diseases (Alzheimer's, Parkinson's, ALS), autoimmune and inflammatory disorders (multiple sclerosis, Crohn's disease, fibromyalgia), as well as chronic viral infections such as HIV. In the management of SIBO, this agent offers a unique dual role by combining prokinetic properties with systemic modulation of the immune and nervous systems.

Physiologically, opioid neurons exert an inhibitory effect on the nerve plexuses in the small intestinal wall, known as tonic restraint. Naltrexone reverses this inhibition, leading to increased acetylcholine (ACh) release and accelerated intestinal transit (Foxx-orenstein et al. 2007). Clinical efficacy in functional gastrointestinal disorders was noted in a pilot study where 0.5 mg of LDN was administered to IBS patients. Symptomatic improvement, particularly a significant reduction in abdominal pain, occurred in 76% of participants (Kariv et al. 2006). In clinical practice, it is important to select the LDN dose based on the patient's predominant symptoms. A retrospective study demonstrated that 2.5 mg twice daily was the most effective regimen in the constipation-predominant subtype, whereas a dose of 2.5 mg once daily proved sufficient in the diarrhea-predominant subtype (Ploesser et al. 2010).

In addition to its effects on motility, LDN binds to the Toll-like receptor 4 (TLR4), which is an important component of the innate immune system. Antagonizing this receptor modulates glial cells, which serve as the resident immune cells of the central nervous system (CNS). In SIBO, endotoxins are often produced by an excessive number of bacteria, leading to chronic activation of these cells and exacerbation of inflammation accompanied by visceral hypersensitivity (Weinstock et al. 2016). LDN suppresses microglial activity and reduces inflammatory cytokine production, potentially alleviating extraintestinal symptoms such as cognitive impairment ("brain fog") and chronic fatigue. These mechanisms suggest that LDN may address broader dysfunction within the gut-brain axis (Ploesser et al. 2010; Weinstock et al. 2016).

Furthermore, a study conducted on a group of patients with active Crohn's disease demonstrated that naltrexone at a dose of 4.5 mg stimulates natural healing and repair processes in intestinal tissues. A significant treatment response was observed in 89% of the participants, and 67% achieved complete clinical remission (Smith et al. 2007).

Despite the promising results, it should be emphasized that the cited data come from a prospective pilot trial conducted on a small group of patients. For this reason, the data obtained are preliminary, and the use of LDN remains an off-label therapy, requiring confirmation in multicenter randomized controlled trials (RCTs).

2.4 Trimebutine

Trimebutine (*Trimebutine maleate*) is a synthetic agonist of the peripheral μ, δ, and κ opioid receptors. Its mechanism of action involves direct effects on the smooth muscles of the gastrointestinal tract and motor dysfunction regulation without affecting the central nervous system. By simultaneously acting on receptors that stimulate motility (μ and δ) and those that inhibit it (κ), it normalizes gastrointestinal peristaltic disorders depending on the functional state of the esophagus, stomach, and intestines (Jo et al. 2024; Chaussade et al. 1987).

This agent exhibits high clinical utility in managing functional disorders, such as dyspepsia. In the results of a network meta-analysis encompassing 25 clinical trials, trimebutine achieved a SUCRA score of 74.5%, ranking as the second most effective intervention, followed only by metoclopramide (Y. J. Yang et al. 2017). Trimebutine is characterized by a high clinical response rate in the treatment of irritable bowel syndrome (IBS), alleviating pain and regulating bowel movements. Studies have shown an improvement in

health status in 56% of patients, which represents a statistically significant advantage over the placebo group, where this percentage was 38% (Chaussade et al. 1987).

The effect of trimebutine on MMC is clinically significant in SIBO adjunctive therapy. Intravenous administration of 100 mg in the fasting state induces Phase III of the MMC, significantly shortening the mean motor cycle duration from 86.4 ± 10.8 min to 32.5 ± 1.0 min. This process occurs through the direct stimulation of peripheral opioid receptors. This is evidenced by the fact that the prior administration of naloxone, an opioid antagonist, abolished the effect of trimebutine (Chaussade et al. 1987).

A recent clinical study published in 2024 in the Journal of Neurogastroenterology and Motility offers a novel perspective on optimizing SIBO treatment. This prospective, randomized, double-blind trial aimed to determine whether trimebutine combined with rifaximin could enhance the efficacy of microbial eradication. This study included patients with functional bloating who had been diagnosed with SIBO using a hydrogen-methane breath test. Data synthesis demonstrated the superiority of the combination regimen. The SIBO eradication rate reached 73.1% in the rifaximin-trimebutine group, compared to 57.1% in patients receiving antibiotic monotherapy. Furthermore, the trimebutine-treated group exhibited a significantly greater reduction in the severity of subjective abdominal bloating (Jo et al. 2024).

This medication has a high safety profile and is well-tolerated by patients. The incidence of adverse effects is approximately 13.1% and does not significantly differ from that of the placebo group, which is 10.3% (Poynard et al. 2001). Side effects are mild and transient, including diarrhea, epigastric discomfort, nausea, and headache (Jo et al. 2024). Such high tolerability allows for the safe use of trimebutine in the long-term prevention of SIBO.

2.5. Itopride

Itopride (*Itopride hydrochloride*) is a modern prokinetic agent that enhances gastrointestinal motility through a dual mechanism of action. Initially, it increases acetylcholine (ACh) release by antagonizing D_2 receptors on cholinergic nerve endings, and concurrently, it inhibits acetylcholinesterase (AChE) in the gastrointestinal smooth muscles (Dite et al. 2014). This results in the stimulation of upper gastrointestinal motility, which manifests as increased pressure in the lower esophageal sphincter, gastric contraction stimulation, and accelerated gastric emptying (Huang et al. 2012; Broeders et al. 2025). Consequently, itopride is a highly effective candidate for managing various upper gastrointestinal motility disorders, including functional dyspepsia and gastroparesis, as well as gastroesophageal reflux disease (GERD). The medication's effect on the distal segments of the digestive tract has also been confirmed experimentally. It stimulates both peristaltic and segmental motility of the large intestine, suggesting a prokinetic effect along the entire length of the gastrointestinal tract (Tsubouchi et al. 2003).

Itopride exhibits a superior pharmacokinetic profile compared to traditional prokinetics, which enhances its clinical safety. It is rapidly absorbed after oral administration, reaching maximum plasma concentration (Cmax) as early as approximately 35 minutes after administration. Bioavailability is approximately 60% due to first-pass metabolism. It binds to approximately 96% of plasma proteins, mainly albumin. Due to its high polarity and low lipophilicity, itopride exhibits negligible crossing of the blood-brain barrier. This prevents central nervous system side effects such as parkinsonism or hyperprolactinemia (Dite et al. 2014; Tonini et al. 2004). Furthermore, its metabolism via flavin monooxygenase (FMO3) instead of the cytochrome P450 system minimizes the risk of drug-drug interactions involving CYP3A4 or CYP2D6 substrates (Huang et al. 2012). The elimination half-life of the compound is approximately 6 hours, and it is excreted from the body along with its metabolites via the kidneys. Itopride does not prolong the QT interval from a cardiac safety perspective, making it a better alternative to older-generation prokinetics that have been withdrawn from the market (Dite et al. 2014). The reliability of this profile has been confirmed in observational studies, which demonstrated the durability and good tolerability of the therapeutic effect during 12 months of treatment. Possible side effects, such as mild abdominal pain or diarrhea, are rare and transient (Broeders et al. 2025). Ultimately, the lack of interaction with cytochrome P450 and the absence of effects on the central nervous system (CNS) make itopride one of the safest prokinetic agents available for patients with gastroenterological conditions.

2.6. Ginger and Prokinetic Herbal Medicine

Ginger (*Zingiber officinale*) has well-documented properties that stimulate muscle contractions, which in turn stimulate peristalsis in the upper gastrointestinal tract. The mechanism of action of ginger is based on a bidirectional effect on serotonin receptors. Active compounds, such as gingerols and shogaols, exhibit antagonism toward 5-HT_3 receptors and agonism toward 5-HT_4 receptors (Hu et al. 2011; Nikkhah Bodagh et al. 2018).

Administration of 1,200 mg of powdered ginger to patients with functional dyspepsia significantly reduced gastric half-emptying time ($T_{1/2}$) from 26.7 ± 3.1 minutes in the placebo group to just 13.1 ± 1.1 minutes. Such a significant improvement in transit dynamics, representing a reduction of over 50%, results from an increase in the frequency of antral gastric contractions. This allows for faster evacuation of food into the duodenum and a reduction in the feeling of fullness (Hu et al. 2011). This effect is even stronger when ginger is combined with artichoke extract (*Cynara cardunculus*). Prodigest® is an example of a supplement that not only accelerates gastric emptying but also reduces stomach volume after a meal (Giacosa et al. 2015).

A phytotherapeutic protocol based on herbs with antibacterial and motility-enhancing properties is as effective as rifaximin in the context of SIBO treatment. Verification using breath tests showed the elimination of bacterial overgrowth in 46% of patients, a result comparable to standard antibiotic therapy, whose efficacy was 34% (Chedid et al. 2014).

Ginger, as a natural MMC stimulator, prevents the accumulation of small intestine contents, which is the main risk factor for SIBO recurrence (Takakura and Pimentel 2020). Additionally, it possesses strong anti-inflammatory properties resulting from the inhibition of cyclooxygenase (COX) and lipoxygenase (LOX) pathways, which supports the regeneration of the inflamed intestinal mucosa. These characteristics make it a safe and effective alternative to synthetic prokinetic agents (Nikkhah Bodagh et al. 2018).

2.7. Compound herbal preparations (STW 5 and STW 5-II)

STW 5 (Iberogast®) is a complex herbal extract consisting of nine plants: bitter candytuft, angelica root, chamomile flower, caraway fruit, milk thistle fruit, lemon balm leaves, peppermint leaves, celandine, and licorice root (Ottillinger et al. 2013; Madisch et al. 2004). The need for long-term use in patients with functional gastrointestinal disorders led to the development of the STW 5-II (Iberogast Advance) formulation. Greater celandine (*Chelidonium majus*) was removed from its composition because of its rare hepatotoxicity potential (Madisch et al. 2004; von Arnim et al. 2007).

The mechanism of action of these preparations is multifaceted and depends on the anatomical region. STW 5 reduces muscle tone and improves proximal stomach accommodation, alleviating early satiety and postprandial pain symptoms (Schemann et al. 2006; Ottillinger et al. 2013). The preparation exhibits a prokinetic effect in the distal part, i.e., the antrum, increasing the force and frequency of muscle contraction. This results in accelerated gastric emptying, reduced fullness, and nausea (Schemann et al. 2006; von Arnim et al. 2007).

In addition to its effects on motor function, STW 5 reduces nerve sensitivity by acting on 5-HT_4 and 5-HT_3 serotonin receptors and M3 muscarinic receptors. It reduces the degree of afferent nerve activation in response to mechanical stretching, which leads to pain relief in patients with functional dyspepsia and IBS (Madisch et al. 2004). The preparation also exhibits anti-inflammatory effects by inhibiting inflammatory mediators, such as leukotrienes and prostaglandins. It stimulates the secretion of protective mucus and bicarbonates, supporting the mucosal barrier's integrity (Ottillinger et al. 2013; von Arnim et al. 2007). In experimental studies, STW 5 prevented increased permeability in the proximal colon and jejunum, as well as in the distal colon, *ex vivo*. Furthermore, the preparation induces significant changes in the microbial composition, normalizing the microbiota, including by reducing the abundance of bacteria of the genera *Clostridium* and *Bacteroidetes* (Allescher et al. 2020).

The clinical efficacy of STW 5 has been confirmed in comparative studies with synthetic agents. A cohort analysis showed that the percentage of patients with complete resolution or improvement of symptoms was higher in the STW 5 group (71.6%) than in the metoclopramide group (62.8%) (Raedsch et al. 2007). Results from randomized trials (ITT population: 308 patients) also confirm a significant advantage of the herbal formulation over placebo in reducing the Gastrointestinal Symptom Score (GIS) during 4 weeks of therapy (von Arnim et al. 2007).

In summary, STW 5 is not a typical prokinetic agent, as clinical trials have not demonstrated an effect on MMC. Its main advantage in SIBO treatment is the effective reduction of accompanying symptoms, such as bothersome bloating, abdominal pain, and a feeling of fullness. In addition, STW 5 supports the regeneration

of the intestinal mucosa affected by bacterial-induced inflammation owing to its strong anti-inflammatory and cytoprotective properties. In clinical practice, it serves as an excellent adjunct to symptomatic treatment, although it is rarely used as the sole agent to prevent the recurrence of SIBO.

Discussion

The treatment of SIBO requires a broader perspective than achieving bacterial eradication. Although antibiotics and dietary changes often quickly alleviate symptoms, the underlying cause of the overgrowth must be addressed with effective and sustained therapy. The high recurrence rate of the condition demonstrates the necessity of combining antimicrobial treatment with MMC stimulation therapy. This approach directly addresses the core of the pathophysiology of SIBO, specifically, the impairment of small intestinal mechanical clearance (Pimentel et al. 2020; Lauritano et al. 2008). Remission maintenance depends on the restoration of phase III MMC function. In cases of its dysfunction, such as due to nerve damage, inflammation, autoimmune diseases, or chronic stress, intestinal clearance slows down or becomes ineffective. Bacteria can accumulate and multiply in the small intestine (Bushyhead and Quigley 2022; Pimentel et al. 2002). Therefore, SIBO therapy increasingly incorporates prokinetics to support digestive motility. The most effective approach is to administer these medications immediately before bedtime, on an empty stomach, at least 3–4 hours after the last meal. This facilitates selective MMC stimulation during the interdigestive state (Usai-Satta et al. 2022; Pimentel et al. 2009). It is precisely the timing of prokinetic administration that determines the success of therapy, as a medication taken too early activates only postprandial transit, which lacks the potential to clear the intestinal lumen (Deloose and Tack 2016).

Emerging evidence challenges the conventional regimen of administering prokinetics only upon completion of antibiotic therapy. Recent research indicates that the synergistic administration of prokinetics and antibiotics significantly potentiates bacterial eradication rates. Stimulating motility during treatment prevents the formation of bacterial reservoirs, which increases bacterial exposure to the antimicrobial agent (Bures et al. 2010; Jo et al. 2024).

Effective relapse prevention requires the precise selection of a prokinetic agent tailored to the specific symptom phenotype. For the Intestinal Methanogen Overgrowth (IMO) phenotype, characterized by predominant constipation, prucalopride remains the therapeutic agent of choice (Pimentel et al. 2006). This substance stimulates 5-HT_4 receptors in the gastrointestinal tract nerve plexuses, thereby significantly increasing intestinal motility. In practice, this agent accelerates intestinal transit, initiates propulsive contractions, and increases the frequency of bowel movements, which directly improves the quality of life of individuals with chronic constipation (Camilleri et al. 2016; Kessing et al. 2014). Prucalopride's neuroprotective potential is also of key importance, particularly in patients with post-infectious damage to the enteric nervous system (Bianco et al. 2016; Liu et al. 2009). A different strategy is required for patients with an irregular bowel movement pattern and those with diarrhea-predominant IBS (IBS-D) with coexisting SIBO. Trimebutine is the most optimal solution in these cases. By simultaneously acting on receptors that stimulate motility (μ and δ) and those that inhibit it (κ), it normalizes gastrointestinal motility disorders, depending on the functional state of the esophagus, stomach, and intestines (Jo et al. 2024; Chaussade et al. 1987). The choice of LDN may be justified in patients with predominant visceral hypersensitivity, as it exhibits anti-inflammatory effects within the mucosa. It should be emphasized that this medication's use in this setting remains off-label (Weinstock et al. 2016; Younger et al. 2014). On the other hand, in the geriatric population, metabolic safety is a priority, which favors itopride. Its negligible penetration across the blood-brain barrier and metabolism independent of the cytochrome P450 system allow for a significant reduction in adverse effects and minimize the risk of clinically significant drug-drug interactions (DDIs) (Huang et al. 2012; Tonini et al. 2004). Table 1. provides the overall summary of the prokinetic agents mentioned.

Table 1. Clinical and Pharmacological Characteristics of Selected Prokinetic Agents

Prokinetic Agent	Mechanism of Action	Dosage	Clinical Phenotype	Safety Profile and Adverse Effects
Prucalopride	Highly selective $5-HT_4$ receptor agonist; exhibits neuroprotective and neuroregenerative properties within the enteric nervous system (ENS).	2 mg once daily; (1 mg in elderly patients or those with renal impairment).	Chronic constipation; Intestinal Methanogen Overgrowth (IMO) phenotype; post-infectious ENS impairment.	High cardiovascular safety. Mild, transient adverse effects: headache, diarrhea, nausea, and abdominal pain.
Low-dose erythromycin	Macrolide antibiotic; acts as a direct motilin receptor agonist.	50 mg administered at bedtime.	Recurrent SIBO with impaired Phase III of the Migrating Motor Complex (MMC); diabetic or idiopathic gastroparesis; cases requiring short-term potent prokinetic stimulation.	Tachyphylaxis due to receptor down-regulation; potent CYP450 inhibitor (high risk of drug-drug interactions); risk of QT interval prolongation; potential for abdominal cramping.
Low-dose naltrexone (LDN)	Transient opioid receptor antagonism inducing a rebound increase in endogenous endorphins; TLR4 antagonist with potent immunomodulatory and anti-inflammatory activity.	1–4.5 mg at bedtime; (titrated dosage).	Predominant visceral hypersensitivity; cognitive dysfunction ("brain fog"); chronic fatigue syndrome.	Vivid dreams, mild insomnia, or transient gastrointestinal disturbances. Excellent safety profile; primarily utilized as an off-label therapy.
Trimebutine	Peripheral μ, δ, κ opioid receptors agonist; acts as a dual gastrointestinal (GI) motility modulator with local anesthetic activity.	100–200 mg three times daily; administered before meals.	IBS-D or IBS-M subtypes with concomitant SIBO; irregular bowel habits, chronic abdominal pain, and visceral discomfort.	Favorable safety profile; lack of central nervous system (CNS) effects or dependence risk. Mild, transient nausea, headache, or rare cutaneous reactions.
Itopride	Dual mechanism: D_2receptor antagonist and acetylcholinesterase (AChE) inhibitor; increases synaptic acetylcholine levels to stimulate upper GI motility.	50 mg three times daily; administered before meals.	Functional dyspepsia (Postprandial Distress Syndrome subtype); gastroparesis; preferred in geriatric populations and patients requiring polypharmacy.	Excellent metabolic safety. Minimal blood-brain barrier (BBB) penetration; negligible risk of extrapyramidal effects. Metabolized by FMO3 (no CYP450 interactions); no risk of QT prolongation.
Iberogast (STW 5 / STW 5-II)	Multitargeted action: dual effect on gastric motility (fundic relaxation vs. antral stimulation). Modulates visceral hypersensitivity via $5-HT_3, 5-HT_4, M_3$ receptors; anti-inflammatory and cytoprotective properties.	20 drops (1 ml) three times daily; administered before or during meals.	Functional dyspepsia and IBS with overlapping symptoms (bloating, fullness, pain); patients requiring mucosal support.	Excellent safety profile. Rare hypersensitivity reactions (rash, pruritus). STW 5-II (reformulated without *Chelidonium majus*) eliminates potential hepatotoxicity risk.

Despite the pathophysiological basis of SIBO recurrence, current knowledge regarding the prevention of this condition has significant gaps and limitations. The most serious problem is the lack of large-scale, head-to-head randomized controlled trials (RCTs) that would directly compare the efficacy of various prokinetic agents. Without such extensive studies, formulating uniform clinical guidelines is impossible. The situation is

complicated by diagnostic ambiguity and the lack of international consensus on whether SIBO recurrence should be diagnosed based on the return of subjective symptoms or on a positive breath test result. This significantly affects the reliability of the available meta-analyses. Most research protocols are limited to short-term observations that typically last up to 12 weeks. This leaves unanswered questions regarding the impact of long-term therapy, lasting several years, on gut microbiome quality and risk of receptor desensitization. The off-label status and lack of standardization in the dosing of certain substances, such as LDN or low-dose erythromycin, also remain a challenge. In the context of phytotherapy, the literature points to the need to verify the ability of STW 5 to induce a state of eubiosis directly in human trials, rather than only in experimental models. From a systems perspective, studies analyzing the interactions between specific types of gases (hydrogen, methane, hydrogen sulfide) and the efficacy of individual pharmacological therapies are lacking. Additionally, the extent to which the presence of polymicrobial biofilm constitutes a mechanical barrier to the action of prokinetic pharmacotherapy and whether MMC activation alone is sufficient to physically disrupt these biological membranes remains unclear. Ultimately, discrepancies in breath test interpretation and inconsistent CFU/mL thresholds in aspirates indicate that patient enrollment in clinical trials is often susceptible to error. These methodological barriers significantly hinder progress in personalizing prokinetic therapy for patients with recurrent SIBO.

Conclusions

SIBO is a disorder characterized by complex etiology and pathogenesis that can be caused by a variety of pathophysiological abnormalities, including anatomical and functional anomalies, as well as adverse effects of pharmacotherapy. The clinical presentation of SIBO is not-specific, and symptoms may overlap with numerous other gastrointestinal disorders. Patient management should be interdisciplinary and multifaceted, encompassing microbial eradication, the implementation of nutritional interventions, and the identification and targeted management of the underlying cause, primarily Phase III MMC dysfunction. Prophylaxis with prokinetic agents is the foundation for the maintenance of remission. The combination regimen, in which a prokinetic is concurrently administered with an antibiotic, achieves the highest efficacy in bacterial eradication, thereby preventing the formation of bacterial reservoirs. Optimal clinical outcomes depend on nocturnal administration of the agent during the interdigestive phase. The selection of a prokinetic agent must be tailored to the clinical phenotype of the patient. Prucalopride is currently the standard of care for long-term prophylaxis due to its high 5-HT_4 receptor selectivity, absence of tachyphylaxis, and cardiovascular safety. An additional advantage is its neuroprotective potential, which supports regeneration of the myenteric plexus. Despite these advances, the lack of standardized criteria for diagnosing relapses and the scarcity of RCTs comparing different prokinetic agents remain key challenges. Further prospective studies are essential to establish optimal diagnostic and therapeutic standards for patients with suspected SIBO and to determine the actual impact of long-term pharmacological MMC stimulation on the composition and function of the human gut microbiome.

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AI: AI was utilized for assistance in refining the academic English language of the manuscript, ensuring clarity, consistency, and adherence to scientific writing standards. It is important to emphasize that all AI tools were used strictly as assistive instruments under human supervision. The final interpretation of results, classification of errors, and conclusions were determined by human experts in clinical medicine and formal logic. In preparing this work, the author(s) used Grammarly for the purpose of checking and improving grammatical correctness. After using this tool, the author(s) have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

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