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Review Article

Prokinetics in the management of upper gastrointestinal motility disorders: an Indian expert opinion review

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ABSTRACT

Functional gastrointestinal disorders (FGIDs) are disorders of gut-brain interaction. Nearly 40% of individuals globally suffer from FGIDs and have chronic fluctuating symptoms. Of all GI conditions, 30-45% are referable to intestinal motility disorders. Prokinetics act by different mechanisms and are effective in FGIDs with delayed gastric emptying or postprandial distress. When choosing a prokinetic, safety is the primary concern, particularly with regard to the central nervous system and cardiovascular risk. Here, we review the efficacy and safety of prokinetics in functional GI motility disorders and provide expert opinions for the use of prokinetics to manage upper GI motility disorders in the Indian context.

Keywords: Functional gastrointestinal disorders, Functional dyspepsia, Prokinetics, India

INTRODUCTION

Functional gastrointestinal disorders (FGIDs) represent a group of disorders of gut-brain interaction. The 2016 ROME IV criteria classify FGIDs based on GI symptoms related to disturbance in motility, alteration in mucosal and immune function and visceral hypersensitivity, changes in gut microbiota, and alteration in central nervous system (CNS) processing.[1] Among these wide ranges of disorders, GI motility disturbances are known to affect a large population worldwide, leading to impaired health-related quality of life and adds to healthcare costs.[2] Population estimates indicate a point prevalence of FGIDs to be nearly 40%. Approximately two-third of individuals with FGIDs suffer from chronic and fluctuating symptoms.[3] Among FGIDs, GI motility disorders are common. Globally, 30%-45% of all GI conditions are referred to as intestinal motility disorders.[4] Though classified as upper and lower GI motility disorders, symptom overlap makes the diagnosis challenging. Diagnosis can be ascertained with GI endoscopy as well as with GI functional tests.[2] The etiology of GI motility disorders is multifactorial and may be idiopathic in most patients.[4] Treatment approaches include dietary modifications, drugs, cognitive-behavioral therapies, and surgical management.[5] Pharmacological options to treat GI motility are varied. Prokinetics enhance motility and reduce visceral pain from gastric distention and can increase postprandial gastric accommodation.[5] Prokinetics act by different mechanisms modulating cholinergic, serotonergic, and dopaminergic pathways.[6] These are more effective in patients with FGIDs having delayed gastric emptying or postprandial distress.[7] However, prokinetics vary in their safety profiles. Given that FGIDs in India are quite common and because they are observed even in school children, it is essential that they are diagnosed in a timely manner and effectively managed.[8,9] Here, we reviewed the current therapeutic

approaches on the management of GI motility disorders with a focus on prokinetics for the Indian context.

METHODOLOGY

Across India, 120 experts on Gastroenterology and Neurology participated in 12 focused group meetings on a virtual platform. One chairperson in each meeting (total of 12) led the evidence-based discussion about using prokinetics to manage upper GI motility disorders. After the discussion on each topic, expert opinions were formulated. After collating the discussion from all meetings, expert opinions were finalized. All participating experts approved the finalized expert opinions.

DIAGNOSING UPPER GI MOTILITY DISORDERS

GI motility disorders can be categorized as upper or lower GI motility disorders. Upper GI motility disorders include achalasia, functional dyspepsia (FD), gastroesophageal reflux disease (GERD), gastroparesis, and biliary dyskinesia.[10] The Rome Foundation global study observed the overall prevalence of any FGID in India to be 7.2%. In this study, the prevalence of functional dyspepsia in the Indian population was 0.7%.[11]

ROME IV criteria classify functional dyspepsia (FD) based on the symptoms. These criteria can be applied in the Indian setting as well. However, there is symptom overlap among the different FGIDs that makes diagnosis difficult. Globally, prevalence of FD varies from 7% to 45%.[12] This number correlates well with that of the prevalence of FD of 7.5%-49% in India.[13] This wide variation in prevalence maybe because of the limited number of studies with ill-defined criteria to diagnose FD.[13] In the Rome IV criteria, postprandial fullness (postprandial distress syndrome [PDS]), epigastric pain syndrome (EPS) and early satiation are considered as "bothersome symptoms." Thus, it involves both EPS, PDS as well as the overlap of EPS-PDS.[14] As indicated by a large population-based study (n=5931) among adults from the USA, Canada, and the UK, PDS (61%) is more common than the EPS (18%) and PDS-EPS overlap (21%).[15] However, in the Indian community, Ghoshal and Singh observed an FD prevalence of 14.7%. Among these individuals, 9% had EPS alone, 27% had PDS, and 64% had EPS-PDS overlap.8 It contrasts with the findings from other countries, indicating a relatively high EPS-PDS overlap in the Indian community. Figure 1 shows the various presenting symptoms of FGIDs the use of pictograms.

Expert opinion

Function GI disorders are commonly encountered in the Indian setup. ROME IV criteria help classify the FGIDs. However, in majority of the patients with FGIDs, there is substantial symptom overlap. In functional dyspepsia, EPS-PDS overlap is the most common presentation that is observed in nearly two-thirds of patients. The use of pictograms may assist in a better understanding of the symptoms.

Decoding the mystery of overlapping symptoms in GERD and FD

In India, the prevalence of GERD varies between 7.6% and 30%, and <10% of these patients have erosive esophagitis.[16] A community-based study from South India observed GERD in 8.2% of individuals. GERD was more common in urban residents, women, and older and obese individuals.[17] Among upper GI motility disorders, GERD and FD often have overlapping symptoms. Differentiating them is essential because they have a substantial impact on patients' quality of life. The symptom overlap is likely to be higher in non-erosive reflux disease (NERD) than erosive disease. Among those with NERD, symptom overlap of FD is highest in patients with functional heartburn. Upper GI endoscopy helps differentiate the different symptoms. The American College of Gastroenterology (ACG) and the Canadian Association of Gastroenterology (CAG) guidelines advocate upper GI endoscopy in adults with FD aged ≥60 years to rule out organic pathology. In adults <60 years, upper GI endoscopy is advised on a case-to-case basis.[18] The Indian consensus identifies that in patients with GERD and those with long-standing symptoms, upper GI endoscopy should be performed at least once in a lifetime. It is also advocated that Helicobacter pylori testing is not routinely needed in patients with GERD.[16] Besides, esophageal manometry helps assess esophageal motor function, and ambulatory pH monitoring helps to document reflux disease in patients with GERD.[19]

Expert opinion

Diagnosis of FGIDs based on clinical symptoms alone is difficult as there is a significant overlap of symptoms. Upper GI endoscopy may help in differentiating the overlapping symptoms. In the diagnosis of GERD or FD, upper GI endoscopy should be done on a case-to-case basis and physicians' clinical judgment whether to investigate or not. Long-standing symptoms, failure of H. pylori treatment, and alarm symptoms may necessitate endoscopic evaluation.

Gastroparesis

Gastroparesis is associated with symptoms of delayed gastric emptying in the absence of physical blockage. Etiologically, it is common in patients with diabetes. A study from India reported gastroparesis in 29% of the patients with longstanding type 2 diabetes mellitus (T2DM). Glycated hemoglobin (HbA1c) and body mass index (BMI) were independent predictors of delayed gastric emptying.[20] In individuals without T2DM, gastroparesis etiology is largely idiopathic. Patients with post-viral infections, Parkinson's disease, collagen vascular disease, post-surgery, intestinal pseudo-obstruction, and other conditions are also associated with

gastroparesis.[21] Hypothyroidism is also being recognized as an important cause of gastric dysmotility.[22]

Diabetic gastroparesis

The prevalence of gastroparesis in patients with diabetes varies from 28% to 65%. There is an intricate relationship between delayed gastric emptying and glycemic levels. Delayed emptying causes altered glycemic control leading to hyperglycemia, which in turn promotes delay in gastric emptying further creating a vicious cycle. It is advised that control of glycemic levels to <180 mg/dL is necessary to avoid gastric motility inhibition.[23]

Diagnosis of gastroparesis

For the assessment of gastric emptying, scintigraphy is the standard test. Gastric retention of >60% of the meal at two hours and/or >10% of the meal at four hours used to confer a diagnosis of gastroparesis.[19] Alternatively, 13C-gastric emptying breath tests can be used to assess gastric motility.[2] Electrogastrography (EGG) is an alternative but may not be available in many centers.

Complications of gastroparesis

Diabetic patients with gastroparesis have unpredictable duodenal food delivery. It may increase the risk of hypoglycemia and hyperglycemic excursions. Furthermore, it may be complicated by bezoar formation especially after bariatric surgery. Small intestinal bacterial overgrowth is evident in nearly 60% of patients with gastroparesis.[24]

Expert opinion

Gastroparesis is common in patients with diabetes. Scintigraphy is a gold-standard test for the diagnosis of gastroparesis. In diabetic patients with gastroparesis, variations in glycemic levels may occur that may result in hypoglycemic and hyperglycemic excursion.

MANAGEMENT OF FGIDs

Approaches to the management of FGIDs are outlined in Table 1.[5,25] Dietary and lifestyle interventions play a vital role in managing FGIDs. Dietary fibers have a beneficial effect on GI motility and act as stool softening and bulking agents. They can increase bloating in a subgroup of patients with PDS. However, maintaining adherence to such regimes is challenging. Patient support programs can be an excellent way to involve patients with FGIDs to ensure compliance with lifestyle modifications over the long term.

PROKINETICS FOR MANAGEMENT OF GI MOTILITY DISORDERS

Prokinetics are the agents that stimulate GI motility. In defining words, prokinetics are a class of agents which enhance coordinated gastrointestinal (GI) motility and transit of content in the GI tract, mainly by amplifying and coordinating GI muscular contractions.[26] Table 2 provides the currently employed prokinetics with their possible indications.[7]

Table 1: Approaches in the treatment of functional GI disorders.

Interventions	Treatments
Dietary and lifestyle	Low lactose diet
	Dietary fibers
	Low fructose diet
	Physical activity
Pharmacological	Prokinetics
	Acid suppressive therapy Antidepressants (e.g., TCAs, SSRIs)
Psychological	Family therapy
	Cognitive-behavioral therapy
	Hypnotherapy

PPIs, proton pump inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants

Dopaminergic antagonists block the D2 receptors in the enteric and central nervous systems. These agents primarily target foregut syndromes.

Serotonergic agonists activate the serotonin receptor (5HT4) on the GI tract. These are considered pan-gut prokinetics.

Cholinergic agonists and acetylcholinesterase inhibitors augment motility throughout the GI tract and can be used for fore-gut as well as for colonic dysmotility.

Motilin receptor agonists had been considered in gastroparesis.

Peripherally acting μ-opioid receptor antagonists are considered for the post-surgical period after large or small intestinal resection with primary anastomosis.

Ghrelin agonist can be used in gastroparesis and chronic constipation.

Prokinetics efficacy in different upper gastrointestinal motility disorders

Prokinetics in FD

The mainstay of treatment in FD is acid-suppressive therapy, and prokinetics are considered as the first choice in those with PDS. Patients who do not respond to acid-suppressive therapy such as proton pump inhibitors (PPIs) should receive prokinetic or tricyclic antidepressants (TCAs). Recent meta-analyses demonstrate that in FD, prokinetics are better than placebo and should be considered in patients who fail to respond to acid-

suppressive therapy.[27] They may be more useful in patients with PDS and EPS-PDS overlap.

Table 2: Prokinetic agents with their possible indications.

Prokinetics	Drugs	Possible indications
D2 antagonists	Metoclopramide	Functional dyspepsia GERD
	Domperidone	Functional dyspepsia Gastroparesis GERD
	Levosulpiride	Functional dyspepsia GERD
	Itopride	Functional dyspepsia GERD Gastroparesis
Serotonergic agonists	Mosapride	Functional dyspepsia GERD Constipation
	Prucalopride	Chronic idiopathic constipation
	Renzapride	Gastroparesis
	Relenopride	Chronic idiopathic constipation
Acetylcholine sterase inhibitors	Neostigmine	Acute colonic pseudo-obstruction Refractory constipation
	Pyridostigmine	Chronic constipation
	Acotiamide	Functional dyspepsia (PDS)
Motilin receptor agonists	Azithromycin	Gastroparesis
Peripherally acting μ-opioid receptor antagonists	Alvimopan	Partial large or small intestinal resection with primary anastomosis (short-term use)
Ghrelin agonist	Relamorelin	Gastroparesis Chronic constipation

GERD: Gastroesophageal reflux disease; PDS, postprandial distress syndrome

Masuy et al reported that the efficacy of prokinetics in PDS is nearly equivalent with responder rates of 59%-81% for dopamine receptor antagonists, 32%-91% for serotonin receptor agonists, and 31%-80% for muscarinic receptor antagonists.[28] In the Indian subset of patients, itopride has equivalent efficacy to domperidone. In patients with non-ulcer dyspepsia, complete symptomatic relief was reported in a non-significantly higher proportion of patients treated with itopride (81%) than domperidone (70%).[29] Another study observed that compared to levosulpiride, moderate to complete symptomatic relief in patients with non-ulcer dyspepsia was significantly higher itopride (90% versus 83.3%, p=0.0146).[30]

Expert opinion

Prokinetics help alleviate FD symptoms and are the first choice in patients with PDS. In patients who fail to respond to PPIs, prokinetics should always be added to acid-suppressive therapy. The efficacy of various prokinetics is nearly equivalent.

Prokinetics in GERD

In patients with GERD, a meta-analysis demonstrated that prokinetics improve gastric motility and improve upper GI symptoms.[31] It is essential, especially in patients with GERD with transient lower esophageal sphincter relaxation (TLESR). TLESR is defined as lower esophageal sphincter relaxation that is induced spontaneously without swallowing. It is an essential mechanism in patients with GERD.[32] TLESR may be associated with an increased esophageal acid exposure caused by increased reflux episodes and increased reflux events.[33] Currently, multichannel intraluminal impedance-pH monitoring (MII-pH) is considered the gold standard for the diagnosis of GERD and TLESR.[34]

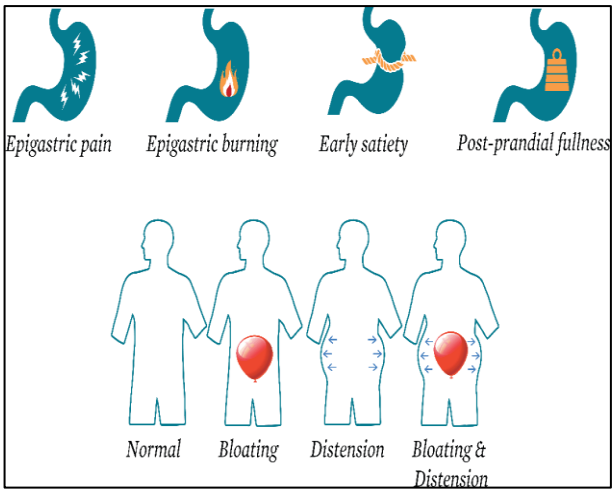

Figure 1: Schematic pictograms to identify the symptoms of functional gastrointestinal disorders.

In patients with GERD, alleviation of symptoms with acid-suppressive therapy does not require further treatment or diagnostic procedures. Acid suppressive therapy, such as with PPIs, relieves symptoms, promotes esophageal

healing, and prevents further complications. However, to maintain remission and prevent relapse, treatment of the root cause of TLESR may be necessary. In case of incomplete response to acid-suppressive therapy, the addition of prokinetic may be helpful, which acts by increasing lower esophageal sphincter pressure and enhancing the esophageal and gastric motility. The 2013 American College of Gastroenterology guideline recommends that refractory patients with objective evidence of ongoing reflux as the cause of symptoms should be considered for additional anti-reflux therapies that may include surgery or TLESR inhibitors.[35]

Prokinetics alone may not provide effective relief in patients with GERD. In combination with PPIs, prokinetics help reduce the number of reflux episodes, results in a greater symptom score change, and may partially improve patient quality of life.[36] Thus, a combination may be preferred when the symptoms are not controlled with PPI alone. In GERD patients with associated PDS, the addition of prokinetics is helpful.

Expert opinion

Prokinetics may be considered in addition to PPIs to alleviate GERD symptoms, to maintain remission and prevent relapse, and to improve the quality of life.

Prokinetics in gastroparesis

Prokinetics are the mainstay of therapy in patients with gastroparesis. In addition to dietary therapy, prokinetics provide symptomatic relief by enhancing gastric emptying.[19] Adequate control of glycemia is necessary for patients with diabetes and gastroparesis. The PROGRESS study involving 41 Indian patients with diabetic gastroparesis, found that treatment with itopride for 8 weeks was associated with significant improvement in gastric symptoms, glycemic parameters, and quality of life.[37] With other prokinetics such as levosulpiride, symptom improvement has been reported without significant effects on glucose levels.[38]

Expert opinion: Prokinetics are the choice of drugs for gastroparesis. One may prefer a prokinetic that helps lower glycemic levels and alleviates gastric dysmotility symptoms.

Choosing a prokinetic

The above discussion indicates prokinetics have nearly equivalent efficacy in FD, GERD, and gastroparesis. Given the equivalent efficacy of different prokinetics, safety is a more important aspect in choosing a prokinetic.

Expert opinion

Safety is a primary concern for choosing among the different prokinetic agents.

Safety of prokinetics

Extrapyramidal side effects

Safety is an important consideration to choose a prokinetic. D2 antagonists that cross the blood-brain barrier are associated with extrapyramidal side effects and an increase in prolactin levels. The propensity of exhibiting these effects varies according to the dissociation constant of prokinetic at D2 receptor compared with that of dopamine. The extrapyramidal side effects may include but are not limited to Parkinsonism or akinesia, acute dystonic reactions or dyskinesias, and tardive dyskinesia. A recent observation from South India in 30 patients with levosulpiride-induced movement disorder identified a significant correlation between the duration of levosulpiride treatment and incidence of tremor/stiffness. Of 19 patients treated with medications, 14 received dopaminergic drugs, of which only one patient had complete recovery after 3 months of therapy.[39] Thus, levosulpiride should be considered in the differential diagnosis of acute onset extrapyramidal side effects while evaluating such patients.

With itopride, the risk of extrapyramidal side effects is minimal. From a meta-analysis of 8 randomized controlled trials, itopride was identified not to have a higher incidence of adverse drug reactions than domperidone, mosapride, or placebo.[40]

Analysis of two placebo-controlled randomized controlled trials observed no extrapyramidal side effects with itopride. Modest prolactin rise was reported in 18% and 0.1% of patients in itopride and placebo groups, respectively. None of the prolactin elevations were severe.[41] TCAs and selective serotonin reuptake inhibitors (SSRIs) also cause extrapyramidal side effects and therefore necessitate careful monitoring for these symptoms.

In routine practice, the true incidence of neurological side effects is difficult to define. It is likely to be underappreciated because of a lack of recognition. In India, prokinetics especially domperidone and levosulpiride were often prescribed as fixed-dose combinations with antacids like PPIs.[42] Also, antacids are the second-most self-medicated drugs after analgesics.[43] Such self-medication behavior increases the potential for adverse effects. Besides self-medication, multiple other factors such as prior history of extrapyramidal side effects, high dose and long duration of treatment, and elderly age increases the risk of extrapyramidal side effects.[44] Identification of the extrapyramidal side effects symptoms may be difficult in an outpatient setting.

Training the patient relative may help pick up abnormal facial movements, facial expressions, and gait changes. Given these concerns, one should choose a prokinetic with the lowest risk of extrapyramidal side effects. Itopride is devoid of central nervous system effects and has minimal

impact on prolactin levels that can be considered a prokinetic of choice to avoid extrapyramidal side effects in patients with FGIDs.[6]

Expert opinion

Extrapyramidal side effects with prokinetics that cross the blood-brain barrier are common and may not be evident easily in day-to-day practice. Patient and relative education to identify the changes in facial expressions and gait can help recognize such side effects. These may be more common in elderly patients, with higher doses and longer duration of therapy. The idiosyncratic reaction may even occur with low doses. Drug holidays may be considered if treatment is continued for 90 days or more. Itopride is devoid of neurological effects, and it may be a choice of prokinetic in patients at risk of extrapyramidal side effects.

Cardiac safety

The cardiovascular effects of prokinetic can occur because of two mechanisms. One is stimulation of cardiac 5-HT4 receptors, and the other is class III-antiarrhythmic properties with some agents.[45] However, agents with increased selectivity for 5-HT4 (e.g., prucalopride) or non-selective agents without any effect on hERG cardiac potassium channel or 5-HT1 receptor (example-Mosapride, and renzapride) are found to be cardiac safe.[46] With domperidone use, a warning is issued about the risk of ventricular tachyarrhythmias and sudden cardiac death. These are more common in doses exceeding 30 mg/day and in those aged >60 years.[47] Concomitant use of other QT-prolonging drugs with domperidone necessitates follow-up electrocardiographic monitoring.[48] A meta-analysis of four studies assessing cardiovascular event risk observed no significant risk of a cardiovascular event at doses of <30 mg/day and 30 mg/day, but a significant increase in cardiovascular risk at doses of >30 mg/day of domperidone.[49] Thus, there is a need for increased awareness of the dosing and monitoring of domperidone to ensure patient safety.

Itopride is not associated with any effects of QTc interval. Studies in healthy volunteers observed results comparable to that of placebo.[50]

Expert opinion

Cardiac effects in the form of prolongation of QTc interval has been reported with some of the prokinetics such as domperidone. Itopride is a cardiac-safe prokinetic. In a subgroup of elderly cardiac patients and patients taking drugs causing prolongation of QTc interval wherein other prokinetics may not be suitable, cardiac safe prokinetic such as itopride may be preferred.

CONCLUSION

Functional GI disorders are common in the Indian population. GI dysmotility such as gastroparesis is observed with increasing frequency in diabetic individuals. Despite advice on dietary and lifestyle changes in FGIDs, poor adherence to these measures requires drug treatment. Prokinetics are effective agents for upper GI motility disorders. Evidence indicates the use of prokinetics is associated with improvement in upper GI symptoms and quality of life. Prokinetics along with acid-suppressive therapy may be preferred in FD and GERD especially in those with reflux disease and PDS. Given their equivalent efficacy, safety is a primary concern when choosing a prokinetic. Being devoid of any central nervous system and cardiac effects, itopride promises to be the choice of prokinetic in most patients with upper GI motility disorders. Itopride may be preferred to other prokinetics for FD in vulnerable groups such as the elderly and patients with diabetes. The expert opinions will assist physicians across the country to effectively manage upper GI motility disorders. In conclusion, a safe prokinetic with equivalent efficacy is needed for effectively treating upper GI motility disorders.

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