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Review Article

Role and safety of prokinetic drugs in the treatment of upper gastrointestinal motility disorders: an Indian perspective

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ABSTRACT

Upper gastrointestinal (GI) motility disorders such as functional dyspepsia (FD), gastroesophageal reflux disease, and gastroparesis are associated with symptoms such as acid reflux, regurgitation, bloating, and heartburn. This review summarizes the prevalence, diagnosis and management of upper GI motility disorders in clinical practice in India, with focus on the use of prokinetics. Lifestyle and dietary modifications, psychotherapy, and pharmacotherapy form the armamentarium for management of motility disorders. Among pharmacotherapies, prokinetics increase gastric emptying and provide symptomatic relief. However, neurological and cardiovascular safety issues are associated with commonly prescribed prokinetics making it important to judiciously select an appropriate drug after weighing out its risk-benefit profile. While metoclopramide, domperidone, and levosulpiride are widely prescribed prokinetics in Indian clinical practice, they are associated with adverse effects such as extrapyramidal symptoms (EPS) and cardiovascular side effects. Itopride, which is a prokinetic with dual mechanism of action, has been found to have equivalent efficacy to other prokinetics and has shown significant improvement in quality of life and symptoms in randomized controlled trials in patients with FD. It acts as a D2 receptor antagonist and acetylcholinesterase inhibitor. Both these actions cause increase in acetylcholine levels, which increases gastric motility. Itopride also has negligible cardiac and neurological safety concerns. Thus, it is a relatively safer molecule compared with other prokinetics, with no EPS or cardiotoxicity concerns and can be used for the long-term management of upper GI motility disorders in a wide pool of patient groups either alone or in combination with other drug classes.

Keywords: Prokinetics, Functional GI disorders, Motility, Itopride

INTRODUCTION

Gastrointestinal (GI) disorders have an organic basis such as inflammatory bowel disease, peptic ulcer, and esophagitis, or can be caused by altered GI motility. Gastroparesis (GP), colonic inertia, diffuse esophageal spasm, and pseudo-obstruction are caused by altered GI motility and abnormal visceral muscle activity. However, more frequently, motility disorders are a subset of functional GI disorders (FGID) that are characterized by chronic or recurrent GI symptoms without structural or biochemical abnormalities.[1] FGIDs are heterogeneous disorders that account for almost one-third of referrals to gastroenterology clinics and are defined in terms of patients' interpretation and self-reporting of symptoms. The Rome IV Foundation describes FGIDs as disorders of gut-brain interaction classified by GI symptoms related to motility disturbances, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota, and altered central nervous system (CNS) processing.[2] A recently published internet and household survey-based global study showed FGID prevalence of >40% among 73,076 adult responders.[3]

In addition to functional disorders, gastroesophageal reflux disease (GERD) and GP are also motility disorders, which can be diagnosed by endoscopic and other examinations. A systematic review and meta-

analysis conducted in 2019 showed a global pooled prevalence of GERD of 13.98% along with a significant economic and societal burden.[4] GP is caused by impaired transit from the stomach to the duodenum without any indication of physical obstruction and is associated with diseases and medications.[5] The negative impact on patient's quality of life and high direct patient and societal costs associated with motility disturbances require suitable treatments to provide symptomatic relief and avoid serious complications.

Treatment approaches for motility disorders are multifactorial due to overlapping symptoms and include lifestyle and dietary modifications, psychological, and pharmacological treatments. Prokinetics help amplify muscular contractions and facilitate peristaltic movements in the gut providing relief from symptoms associated with inadequate gastric emptying.[6] They produce their effects on dopaminergic, serotonergic, and cholinergic receptors and modify the secretion of different neurotransmitters that control peristalsis.

Epidemiological studies conducted in India reveal a relatively high prevalence of FGIDs at about 21.7%-26.9% in two studies in rural and college patients, respectively, with FD being the most common FGID.[7,8] Furthermore, the Rome Foundation Global study from 2021 also showed an FGID prevalence rate of 7.2% (95% CI: 6.5-8%) through household surveys conducted in India.[3] Considering the high prevalence of motility disturbances, this review aims to collate information related to the use of prokinetics in India and the opinions of physicians regarding their clinical use and safety.

Across India, 12 focus group meetings, with 144 experts in the field of Gastroenterology were conducted in-person and on virtual platforms. One chairperson in each meeting led the discussion. After each meeting, expert opinions were collated, finalized, as well as formulated taking into consideration the consensus from each meeting.

UNDERSTANDING OF UPPER GI MOTILITY DISORDERS

Upper GI motility disorders are caused by abnormal muscle and nerve contractions in the upper part of the GI tract leading to acceleration or delay in GI transit. Achalasia, GERD, GP, dumping syndrome, FD, cyclic vomiting syndrome, and cannabinoid hyperemesis syndrome are some upper GI motility disorders. Although the diagnosis of a particular disorder is based on prominent symptoms, diagnostic tests, and endoscopic evaluations, it is common to find coexistence of conditions due to similar underlying pathophysiology. Overlapping symptoms between different disorders include nausea, vomiting, heartburn, bloating, regurgitation, epigastric pain, and discomfort. GERD-FD commonly occur together with an overlap of 22.9%-51.3% in Western and Eastern populations causing a higher symptom burden and healthcare visits than any individual condition.[9,10] Symptom similarity between GP and FD also leads to challenges in diagnosis wherein a study showed that 90.8% of GP patients fulfilled FD criteria on a Rome IV diagnostic questionnaire.[11] Overlaps between symptoms of upper GI motility disorders stem from their common pathophysiology making it difficult to separate out and understand the underlying disorder and treatment options.

Expert opinion

FGIDs occur frequently in Indian patients with FD. Although the ROME IV criteria classify FD as FD-EPS (epigastric pain syndrome) and FD-PDS (postprandial distress syndrome), there is significant overlap between the symptoms making subtype differentiation questionable from an Indian patient perspective. Symptom severity, pattern, and frequency are defined differently globally making it important for diagnosis to be country specific. Additionally, pictograms can be used to assist patients to identify and pinpoint symptoms accurately allowing for appropriate management. Other common upper GI motility disorders are related to esophageal motility such as achalasia and can be diagnosed by esophageal manometry, swallowing tests, and clinically relevant symptoms.

DYSPEPSIA: DIFFICULTIES IN DIAGNOSIS AND MANAGEMENT

Dyspepsia (bad digestion) is characterized by symptoms in the upper abdomen such as fullness, discomfort, early satiation, bloating, belching, nausea, vomiting, and pain. Dyspepsia can be divided into two classes: organic, caused by peptic ulcers, GERD, pancreatic or biliary disorders, infections, or cancer; and FD, which accounts for 50%-60% of dyspepsia cases.[12] The Rome IV Foundation divides FD into postprandial distress syndrome (FD-PDS) characterized by early satiation and postprandial fullness and epigastric pain syndrome (FD-EPS) with features of pain or burning sensation in the epigastric area unrelated to food intake with symptoms for at least 3 months and negative endoscopic findings.[13] Vakil et al showed prevalence rates of FD-PDS of 10%, of FD-EPS of 24%, and EPS-PDS overlap of 66%.[14] Wide variations in the prevalence of dyspepsia from 10% to 30% in different geographical locations can be attributed to epidemiological differences (gender, race, or age), socioeconomic considerations, dietary and lifestyle factors, and different diagnostic criteria.[15]

The underlying pathophysiology of FD is complex and involves a combination of several factors of which altered motility is significant and occurs in 20%-50% of patients with FD.[16] Gastric and duodenal hypersensitivity, *Helicobacter pylori* infection, duodenal inflammation, environmental exposure, and psychosocial factors also play a role in the pathogenesis of FD. Risk factors for FD include female gender, alcohol, smoking, and the use of

non-steroidal anti-inflammatory drugs (NSAIDs).[3] Symptom overlap, and coexistence of reflux diseases and IBS with FD make diagnosis difficult.

Prokinetics promote gastric motility, increase gastric emptying, and prevent reflux and retention of gastric contents and are recommended as first-line treatment for patients with FD-PDS.[17] Reduction in dysmotility symptoms of early satiety and postprandial fullness have been observed during treatment with prokinetics such as metoclopramide, domperidone, cisapride, and mosapride. In contrast to the mentioned prokinetics, itopride has a dual mechanism of action as a dopamine D2 receptor antagonist and acetylcholinesterase inhibitor. Both these actions cause an increase in acetylcholine levels, which increases gastric motility, accelerates gastric emptying, and coordinates gastroduodenal contractions. Itopride has shown significant improvement in quality of life and symptoms compared with placebo and equivalent efficacy to other prokinetics in randomized controlled trials in patients with FD with negligible cardiac and neurological safety concerns.[18]

Expert opinion

Overlap of symptoms between different disorders such as FD, IBS, and GERD and different types of FD make diagnosis challenging despite the development of Rome IV criteria. Diagnosis algorithm for FD involves *H. pylori* testing, endoscopic evaluation, esophagogastroduodenoscopy (EGD), and gastric biopsies depending on patients' age and risk factors to rule out organic causes. Although *H. pylori* testing is recommended in patients <60 years, a high percentage of Indians test positive for *H. pylori* making this test inconclusive. Accessibility to non-invasive *H. pylori* testing may also be limited. Endoscopy is recommended in patients >60 years and those with alarm symptoms. Prokinetic treatment algorithm for FD patients was discussed: patients with FD-PDS are expected to show a better response to prokinetics (with or without proton pump inhibitors [PPIs]) and itopride is regarded as the most favorable prokinetic with acceptable efficacy and minimal to no adverse effects.

DILEMMA BETWEEN FD AND GERD: DIAGNOSTIC AND TREATMENT CONSIDERATIONS

The coexistence of GERD and FD occurs more frequently than expected by chance in patients, indicating a common pathophysiology. GERD is caused by the backflow of stomach contents into the esophagus due to compromise of the lower esophageal sphincter (LES), which causes symptoms of heartburn, acid reflux, and regurgitation. Approximately 40% of patients with FD have impaired gastric accommodation causing LES relaxations resulting in GERD-FD overlap.[19] A meta-analysis conducted in 2020 showed a global prevalence of FD-GERD overlap of 7.4%. There was a significant symptom overlap with 41.2% of FD symptoms in GERD patients, and 31.3% of GERD symptoms in the FD patients.[20]

Common underlying pathophysiological mechanisms between GERD and FD namely, acid reflux, abnormal GI motility, psychosocial issues, genetics, and diet are responsible for overlapping symptoms.[10] A study by Quach et al showed that FD-PDS is more prevalent among patients with FD-GERD overlap and NERD-FD overlap, causing more severe symptoms.[21] First-line treatment for GERD patients are acid-suppressive treatments such as PPIs or histamine H2-antagonists in conjunction with dietary and lifestyle modifications. Despite this, a considerable proportion of patients with some types of GERD do not experience symptomatic relief.[22] Since motility disturbances are implicated in GERD, the use of prokinetics has been suggested in conjunction with PPIs/H2-antagonists for GERD-FD overlap patients. Prokinetics, also act by increasing the LES pressure, which increases the gastric emptying rate and is of significance in reflux episodes associated with transient relaxation of the LES. Several meta-analyses have shown a significant improvement in symptom response, greater symptom relief, or improvement in quality of life with prokinetics plus PPIs versus PPI monotherapy based on questionnaire responses.[23]

Expert opinion

Based on high prevalence and increased symptom burden of FD-GERD overlap over any single condition, combined treatment with PPIs and prokinetics was recommended by the panelists, with itopride being chosen as the most favorable prokinetic. Lifestyle interventions can help relieve mild symptoms. Endoscopic evaluations, pH monitoring, and esophageal manometry can help detect acid reflux. Non-responsiveness to PPI treatment indicates a dyspeptic component or NERD and warrants investigations by specialists. Additional pH testing is necessary if reflux symptoms are not controlled with PPIs. Since relaxation of lower esophageal sphincter is associated with reflux episodes, prokinetics are expected to help by increasing the LES pressure.

DIABETIC GASTROPARESIS: DIAGNOSIS AND MANAGEMENT OF MOTILITY DISORDERS IN DIABETICS

GP is defined as the impaired transit of intraluminal contents from the stomach to the duodenum in the absence of mechanical obstruction leading to early satiety, postprandial fullness, nausea, vomiting, anorexia, and weight loss.[5] Most GP cases are idiopathic (50%) or associated with diabetes (25%), post-surgical complications, neurological diseases, and infections.[5,15] Delayed gastric emptying in diabetic patients is caused by damage to the vagus nerve and pacemaker cells causing diabetic gastroparesis (DGP) leading to uncontrolled

glucose levels and hyperglycemia.[24] DGP affects 20%-50% of the diabetic population and occurs more frequently in patients with type 1 diabetes (T1D; 4.8%) than type 2 diabetes (T2D; 1%), and much more in diabetics than in the general population (0.1%). A study from India showed delayed gastric emptying in 29% of patients with T2D, which was positively correlated with higher glycated hemoglobin (HbA1c) and body mass index.[25]

Diagnosis of DGP involves a thorough evaluation of the patient's medical history, laboratory investigations, endoscopy, and gastric emptying studies, such as scintigraphy tests using radiolabeled colloids and wireless motility capsules, breath tests, and gastroduodenal manometry. Nutritional support, lifestyle and behavioral interventions, glycemic management, and prokinetics help manage the cyclical relationship between poor glycemic control and slow gastric emptying. Prokinetics are the cornerstone for the management of GP as they increase gastric contractility and allow for rapid stomach emptying. Meta-analyses showed that prokinetics caused a significant reduction in HbA1c levels compared with placebo in patients with T1D and T2D and improved gastric emptying, thereby providing symptomatic relief.[26] Itopride results in increased gastric motility and LES pressure, accelerated gastric emptying, and improved gastroduodenal contraction and is recommended for DGP.[27] Significant improvement in glycemic indices and improved quality of life has also been associated with itopride use.[28]

Expert opinion

Prokinetics like itopride remain the mainstay for treatment of DGP based on results from the PROGRESS study in India wherein an improvement in GI symptoms, glycemic control, and quality of life was observed with itopride use.[28] Diagnosis of GP is based on gastric scintigraphy, which involves gastric emptying of solids and remains the gold standard for diagnosis of DGP. Lack of testing facilities as well as the infrastructure in India make diagnosis challenging. There is also limited training and skill in the interpretation of electrogastrography (EGG), which is used for the diagnosis of the DGP.

ACID REFLUX AND NOCTURNAL ACID BREAKTHROUGH: MANAGEMENT APPROACH AND TREATMENT OPTIONS

Transient relaxation of the lower esophageal sphincter (TLESR) causes acid reflux and the classic symptoms of heart burn and regurgitation. GERD is a chronic and more severe form of acid reflux. Management and treatment options for acid reflux include PPIs and H2-blockers, over-the-counter antacids, prokinetics, tricyclic antidepressants, pain modulators, dietary modifications, and lifestyle changes.

Nocturnal acid breakthrough (NAB) is defined as gastric acid recovery to a pH level <4 for at least 60 consecutive minutes in the overnight period when on PPI treatment independent of PPI type.[29] Various factors such as the short serum half-life of PPIs, activation of proton pumps at different times, and regeneration of proton pumps during the overnight period cause NAB. The clinical impact of NAB is particularly relevant in patients with GERD, Barrett's esophagus, and esophageal motility abnormalities. A study by Katz et al showed that NAB occurred in 70% of subjects with GERD, 80% with Barrett's esophagus, and only 8% of normal controls.[30] Pharmacological management of NAB involves adjustment of the timing, dose, and frequency of PPI administration and addition of H2-receptor antagonists. Several studies have shown an improvement in occurrence and duration of NAB following twice daily and evening administration of PPI, treatment with PPIs with longer half-lives, and the addition of H2-receptor antagonists.[31] Alginate-based therapies, which form a floating raft of gel and localize the acid pocket in the proximal stomach, have been shown to be superior in controlling mild GERD symptoms versus placebo or antacids and can be used alone or in combination with PPIs/H2 blockers.[32]

Expert opinion

NAB is a poorly understood but frequent complication that is of relevance in patients with GERD and is an expected phenomenon of PPIs. Treatment compliance is of utmost importance along with up dosing to twice daily PPIs or addition of H2-blockers at bedtime. Prokinetics and baclofen are also suitable alternatives to PPIs in cases of reflux refractory to PPIs. Experts expressed interest in the use of alginates for providing immediate and long-lasting relief from acid reflux symptoms and considered it to be a safer option in sensitive groups such as pregnant women and NERD patients either as monotherapy or combination therapy. Newer PPIs like lansoprazole delayed release or tenatoprazole may be effective but warrant further investigation.

UNDERSTANDING THE ROLE OF PROKINETICS AND THEIR SAFETY IN MOTILITY DISORDERS

Appropriate pharmacological management of upper GI motility disorders can be achieved by targeting cholinergic, dopaminergic, and serotonergic receptors. Prokinetics are often prescribed for the treatment of motility disorders. They act by stimulating the release of excitatory neurotransmitters such as acetylcholine and suppressing the release of inhibitory neurotransmitters such as dopamine and serotonin.

Table 1 contains information on the different classes of the prokinetics along with their mechanisms and indications. Despite their favorable efficacy in several trials, the safety of the several prokinetics remains a concern.[33-36]

Table 1: Prokinetics in upper GI motility disorders.

Pharmacological class	Mechanism of action	Drugs	Indications
Dopamine antagonists (D2 antagonists)	Block D1, D2 and D3 receptors, inhibit release of DA and improvement in LES tone and gastric tone, partial 5-HT_4 receptor agonism that stimulates cholinergic pathway[33]	Metoclopramide, domperidone, levosulpiride, itopride	FD, diabetic GP, GERD
Serotonergic agonists	Act on 5-HT_1, 5-HT_3, and 5-HT_4 receptors and increase Ach and nitric oxide that increase peristaltic contraction and relax gastric fundus[34]	Cisapride, tegaserod, renzapride, prucalopride, mosapride, buspirone	GERD, FD, chronic constipation
Cholinergic agonists	Stimulation of M2-muscarinic receptors on smooth muscles and inhibition of Ach metabolism[35]	Bethanechol, neostigmine, pyridostigmine	GP, FD, constipation
Motilin receptor agonists	Facilitate Ach release from cholinergic neurons in the gut which stimulates gastric emptying[36]	Azithromycin, erythromycin	GERD, diabetic GP
μ-opioid receptor antagonists	Block peripheral μ-opioid receptors and stimulate peristalsis	Alvimopan	Chronic constipation
Ghrelin agonists	Increased GI motility and gastric emptying via stimulation of vagal signaling	Relamorelin	Diabetic GP

Ach: acetylcholine; DA: dopamine; LES: lower esophageal sphincter; FD: functional dyspepsia; GERD: gastroesophageal reflux disease; GP: gastroparesis

Cardiovascular safety issues

Cisapride, a partial 5-HT4 receptor agonist indicated for treatment of GERD, dyspepsia, and GP, was withdrawn from the market in 2000 due to reports of cardiac arrhythmias and death. The effect of cisapride on 5-HT4 receptors in the heart and urinary bladder led to tachycardia, urinary incontinence, and prolongation of cardiographic QT interval.[37] Other 5-HT4 agonists such as tegaserod are also associated with cardiovascular side effects. Currently, prucalopride and mosapride that have selective 5-HT4 activity and low affinity for other 5-HT receptors and hERG-potassium channels are approved for the treatment of GERD and FD.[38] Domperidone, a peripheral D2 receptor blocker also causes QT prolongation leading to ventricular arrhythmia and death, which led to its withdrawal from the market in several countries and issuance of a 'black box' warning to its labeling.[39] A meta-analysis showed a significant increase in QT prolongation events at domperidone doses of >30 mg/day compared with placebo.[40] In addition to cardiovascular side effects, treatment with domperidone is linked to gynecomastia, galactorrhea, amenorrhea, and impotence caused by D2 blockade in the pituitary.

Itopride, approved in Japan, Western European countries, and India for the treatment of FD by promoting GI motility, has no effect on QT interval prolongation and has been shown to be cardiac safe in several studies.[18]

Neurological safety issues

Blood-brain barrier (BBB) permeability and antagonism of central D2-receptors are responsible for drug-induced movement disorders (DMIDs) associated with the use of some prokinetics.

Metoclopramide is a D_2 receptor antagonist used for the treatment of diabetic GP. Extrapyramidal side effects such as tardive dyskinesia, restlessness, akathisia, insomnia, agitation, drowsiness, fatigue, and dystonic reactions have been associated with its use. Children and young adults as well as women are more susceptible to the adverse effects of metoclopramide, which shows a dose-dependent behavior.[41] Furthermore, increased prolactin secretion caused by metoclopramide has led to breast engorgement, galactorrhea, and irregular menses. Case reports related to adverse effects such as dystonic reactions associated with metoclopramide use have been reported in India.[42]

Levosulpiride, which has a high affinity constant for central D2 receptors is associated with the development of parkinsonism and is shown to progress to irreversible parkinsonism when used individually or with PPIs.[43] Other extrapyramidal adverse effects caused by levosulpiride include tardive dyskinesia, acute muscular dystonia, akathisia, isolate tremor, and hemichorea.[44] Elderly patients, females, and those with kidney diseases are susceptible to the side effects of levosulpiride necessitating dosage adjustment or alternative treatments.[45] Unlike these drugs, the high polarity of itopride prevents it from crossing the BBB, and it is devoid of CNS adverse effects making it a safer option than other prokinetics. Additionally, itopride does not exhibit pharmacokinetic drug interactions with CYP450 enzyme inhibitors like macrolides and azole antifungals allowing for concomitant use with these drugs.[27]

Expert opinion

Although most prokinetics show equivalent efficacy, the decision to use a particular prokinetic must be made following a thorough evaluation of its risk-benefit profile. The panelists converged on the use of itopride as a safer option in motility disorders based on promising data from several trials conducted in India.

As several prokinetics cause DMIDs, it is essential for comprehensive neurological and psychological monitoring of patients and judicious use of these drugs. Patients and physicians should stop treatment on suspicion of any neurological side effects and shift to a safer medication. Various factors such as age, gender, co-administration of QT prolonging drugs, underlying diseases, and market availability and cost of the drug must be considered before prescribing a particular prokinetic, and treatment must be individualized as per patient profile.

PERSPECTIVE ON THE CNS EFFECTS

Neurological side effects and extrapyramidal reactions of metoclopramide are common. Adverse reactions such as irritability, drowsiness, dyskinesia, dystonia, convulsions, hypertonia, and tremors are seen in <0.01%-23% of patients on metoclopramide and can be attributed to chronic use of metoclopramide, high doses of >30 mg/day, and advanced age.[46] The USFDA has placed a black box warning on metoclopramide, limiting its use to a shorter time and at lower doses for GI disorders. Parkinsonism-like symptoms have been observed following recurrent, chronic use of metoclopramide, whereas acute dystonic reactions have been seen after a single dose of metoclopramide within 24 h of administration.[47]

Like metoclopramide, neurological adverse effects have also been noticed following oral administration of levosulpiride. A study from India that analyzed 30 patients with levosulpiride-induced movement disorders found a direct correlation between the duration of treatment and tremors and stiffness a few days to a few weeks after treatment.[48] Levosulpiride is associated with the development of parkinsonism-like symptoms, which are shown to persist even after withdrawal of the drug. Case reports have also shown the development of dystonic symptoms in patients treated with levosulpiride for varying lengths of time. Therefore, it is necessary for physicians to be aware of these movement disorders before prescribing levosulpiride along with the provision of a warning label for these effects.[44]

Although mosapride (a selective 5-HT4 agonist), which was developed as an alternative to cisapride, is devoid of cardiotoxicity, case studies have shown the development of tardive dyskinesia and drug-induced parkinsonism in three elderly patients. This indicates that although mosapride does not act on dopamine receptors it can possibly enter the CNS with an effect on nigrostriatal dopaminergic receptors.[49]

Domperidone's inability to cross the BBB is generally associated with a lack of CNS side effects despite its action on peripheral and central D2 receptors. However, recent reports on the development of acute dystonia following domperidone usage in children have been reported, which was reversed following drug discontinuation and anticholinergic administration.[50] The occurrence of dystonia in the pediatric population can be attributed to the poorly developed BBB.

Expert opinion

BBB permeability and high dissociation constant of drugs such as metoclopramide and levosulpiride at central D2 receptors are responsible for their extrapyramidal side effects such as tardive dyskinesia and parkinsonism, respectively which persist even after drug discontinuation. Comprehensive neurological and psychological examinations are necessary to determine the extent of drug-induced disability and to decide on temporary stoppage (drug holidays) or discontinuation. It is essential for close monitoring and recognition of DMIDs. The panelists agreed that levosulpiride should be used with caution especially in susceptible groups such as females, elderly patients, and those with chronic kidney disease especially in India where levosulpiride and PPIs are available as fixed-dose combinations for long-term use. Furthermore, they all recommended itopride for FD based on its better safety profile as it is devoid of EPS and hyperprolactinemia and can be potentially used for a longer duration.

CONCLUSION

The high prevalence of FGIDs globally and particularly in India necessitates suitable lifestyle measures as well as pharmacological treatments for symptomatic relief and resolution. In addition to mainstay drugs such as PPIs and H2-blockers, prokinetics have also gained increased attention for treatment of FD, GERD, and DGP as they are all associated with motility disturbances. Among prokinetics, metoclopramide, domperidone, and levosulpiride are prescribed widely but are associated with adverse effects such as DMIDs, cardiovascular side effects, galactorrhea and hyperprolactinemia. Unlike these prokinetics, itopride is a relatively safer molecule with no EPS or cardiotoxicity concerns and can be used for the long-term management of FGIDs in a wide pool of patient groups either alone or in combination with other drug classes. Itopride appeared to be the preferred choice of prokinetics amongst panelists from pan India for the management of upper GI motility disorders.

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