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Integrated Approach to Disorders of Gut-Brain Interaction: Place of Prokinetics and Combinations with Proton Pump Inhibitors

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ABSTRACT

It is being increasingly recognized that there is a considerable overlap between clinical presentation and symptoms of upper and lower gastrointestinal (GI) disorders. An integral connection of the gut receptors and the brain has also been shown now. Though the term 'functional' GI disorders has been in use for long, it is now understood and accepted that factors like visceral hypersensitivity, central sensory dysregulation, GI dysmotility, alteration of the gut flora, GI inflammation with changes in barrier function and gut immunity, as well as presence of psychosocial factors may all have a role to play. Therefore, the new term 'disorders of gut-brain interaction' (DGBI) has been suggested. In this context, it is important to understand the place and appropriate usage of prokinetics and their combinations as these are available and prescribed commonly in India. Recognizing overlap of GI symptoms, and understanding the gut-brain receptors with relevance to the action of prokinetics, can help make rational treatment decisions and selection of appropriate pharmacotherapy.

Keywords: Gut-brain, overlap, GERD, dyspepsia, constipation, dysmotility, prokinetic

In the wake of the recent Rome IV guidelines and repeated evidence of upper and lower gastrointestinal (GI) symptom overlap, the concept of approaching the same as disorders of gut-brain interaction (DGBI) has been recommended.[1]

A panel discussion called the 'Resync GI panel' of experts in the field of Gastroenterology was done for an integrated management of GI disorders by 'syncing' the brain, upper and lower GI as a unified system, and understand therapeutic options which are in sync with this concept with special reference to prokinetics and their combinations with proton pump inhibitors (PPIs). The detailed literature review and panel discussion is presented in two parts: understanding the upper GI-lower GI–brain connect and pharmacological management of GI disorders.

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UNDERSTANDING THE BRAIN-UPPER GI-LOWER GI CONNECT

Gastrointestinal nerve supply comprises of myenteric and submucosal plexus, parasympathetic supply from vagus nerve (till proximal colon) and distally by sacral nerves and sympathetic nerve supply from T6 to T9 and L2 to L5.[2] The various GI receptors are summarized in Table 1.[3-6]

Summary Comments from the Panel

- *Due to the presence of 5-HT4 receptors throughout the GI tract, prokinetic drugs with 5-HT4 agonistic action can improve motility of both upper and lower GI tract.*
- *Drugs inhibiting D2 receptors or 5-HT3 receptors will additionally act on chemoreceptor trigger zone (CTZ) to prevent vomiting. Drugs with selective D2 receptor antagonistic action mainly improve upper GI motility.*
- *Cholinergic receptors are present throughout the GI tract but their density decreases as we move from proximal to distal colon. Prokinetic drugs acting on these receptors as*

Table 1. Summary of GI Receptors

Important GI receptors with location	Function
Cholinergic receptors[3]	Increase LES tone
Mainly M3 and lesser extent M2 throughout GI tract (more in upper GI) - Density decreases as we move from proximal to distal colon	Increase peristalsis and gastric emptying
	Increase intestinal motility
	Increase GI secretions
	Act centrally to decrease vomiting
Adrenergic receptors[4]	Decrease peristalsis, gut motility and GI secretions
Alpha1, beta1 and 2 - GI smooth muscles	
Dopaminergic receptors[5]	Inhibit acetylcholine release - decrease LES tone and esophageal peristalsis
Mainly D2 receptors in upper GI - esophagus, stomach, CTZ and brain	Cause of nausea and vomiting
	Decrease gastric emptying
Serotoninergic receptors[6]	Increase sphincter tone (LES)
5-HT4 (throughout GI tract) - acts on proximal GI through acetylcholine release (contracts longitudinal muscle) and on distal GI by directly relaxing circular muscle	Increase peristalsis
	Increase gastric emptying
	Increase intestinal motility
	Increase GI secretions
5-HT3 (CTZ and vomiting center, enteric neurons)	Induces vomiting and increases secretions and motility

agonists are more effective in upper GI especially in gastric emptying.

- *Knowledge of the GI receptors as well as the mechanism of action of various GI motility drugs on these receptors is very crucial in selecting the appropriate therapy for particular subsets of patients.*

As per Rome IV recent criteria, bowel disorders exist as a continuum rather than as independent disorders. The guidelines recommend doing away with the 'functional' word and have now given the term as 'disorders of gut-brain interaction' thereby establishing a hypothesis of upper GI-lower GI-brain connect.[1] Therefore, gastroesophageal reflux disease (GERD), functional dyspepsia (FD), chronic constipation and irritable bowel syndrome (IBS), etc. are different clinical manifestations of disordered functioning of the GI tract (Fig. 1).[7]

In both FD and IBS, the pathophysiology is likely to be mixed.[8] There is a significant overlap of the pathophysiological mechanism which forms the basis of

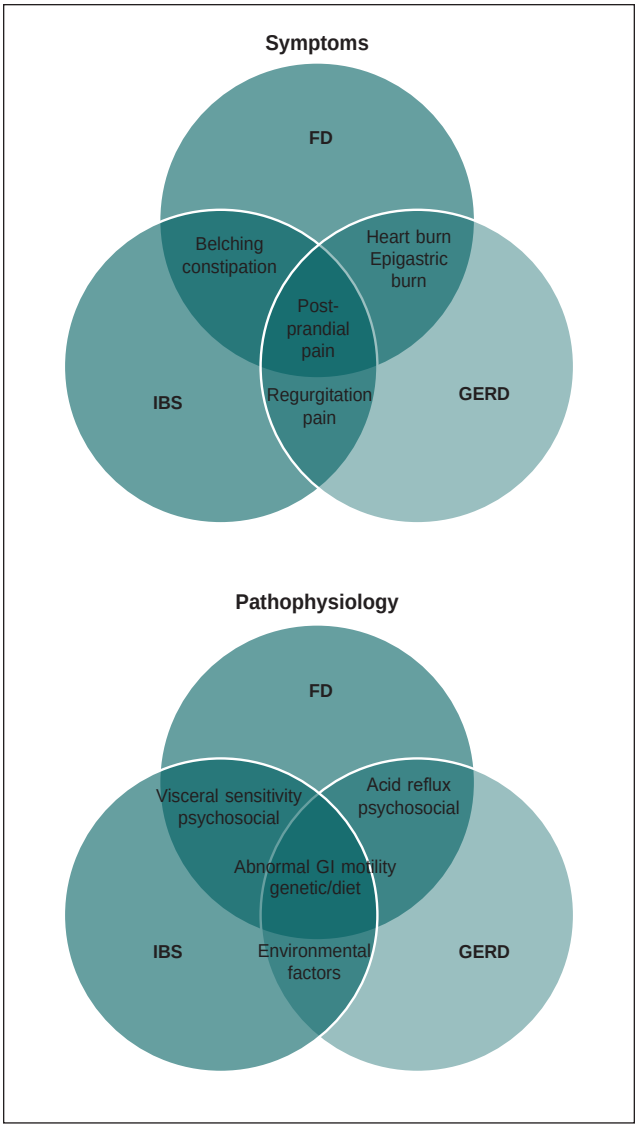

Figure 1. Different clinical manifestations and pathophysiology of disordered function of the GI tract.[7]

functional bowel disorders by both FD and IBS.[9] Levels of evidence are maximum for intestinal dysmotility and visceral hypersensitivity for both IBS and FD, however, central sensory dysregulation, alteration in GI flora, GI inflammation and psychosocial factors may also play a role.

Summary Comments from the Panel

- *Based on clinical experience and patient presentation, upper GI and lower GI exist in continuum and not as separate entities.*
- *The recent Rome IV has given clear objectives and removed subjective components and terminologies (like 'functional' and 'discomfort').*
- *Investigating the patient thoroughly, (with special emphasis on GI allergies) as well as studying diet and nutrition, lifestyle*

factors and intake of drugs (nonsteroidal anti-inflammatory drugs [NSAIDs], etc.) was recommended before labeling GI disorders as 'functional'.

- *Visceral hypersensitivity, gut microbiota, local immunity and inflammation, GI barrier function and a psychogenic component play an important role in these disorders.*

Prevalence of Overlap of GERD, IBS, FD: What does the Literature Say?

Overlap rate of FD-IBS is in the range of 11-27%.[8,10] In population-based studies, the estimated prevalence of IBS among dyspeptic subjects, ranges from 13% to 29%, while the prevalence of FD among IBS subjects ranges between 29% and 87%.

In-patient-based series, as opposed to community series, the prevalence of overlap was shown to be even higher with 26-46% of FD patients having concomitant IBS and as many as 87% of IBS patients having concomitant FD. In a population-based study from Mumbai, India, the prevalence of dyspepsia was 30%, while among subjects with IBS, the prevalence of dyspepsia was 58%. In another study from India by Goshal et al, about 50% patients showed an overlap of FD-IBS. GERD and IBS symptoms were both found in dyspeptic patients in 16-32% cases.[11]

The prevalence of IBS, among subjects with dyspepsia at 14% was greater than in the general population where it was 7.5%. The frequency of FD, IBS and FD-IBS overlap was found to be 53%, 21% and 1.6%, respectively.[12,13] In Asia, Shah et al found that 58% of subjects with IBS had dyspeptic symptoms, 14% of subjects with dyspeptic symptoms had IBS. It was seen that 41.4% had visited a physician for their complaints and 40% received treatment with antacids, acid suppressors or a prokinetic drug.[13]

Door-to-door survey in a rural Indian population revealed that 21.7% had GI symptoms (dyspepsia: 14.9%, IBS: 2.7% and dyspepsia-IBS overlap: 4.1%). Dyspepsia patients more often had overlap of epigastric pain and postprandial distress rather than any specific subtype. Chewing tobacco, intake of aerated soft drink, intake of coffee/tea, disturbed sleep, vegetarianism and anxiety parameters were associated features. It was seen that dyspepsia was a predictor of IBS and abdominal bloating was often associated with dyspepsia and dyspepsia-IBS overlap.[14]

Summary Comments from the Panel

- *In clinical practice, overlap between upper and lower GI symptoms in patient presentation is very high and underestimated in studies. In actual practice, the overlap is in up to 80-90% patients.*
- *There is a significant amount of data among Asian populations especially in Japan as well as in India which show overlap of GERD, IBS and dyspepsia showing their existence as a continuum and not distinct disorders.*

Mechanism Underlying GERD and Dyspepsia

The mechanisms underlying reflux in GERD include frequent TLESRs (transient lower esophageal sphincter relaxations) as seen in day burpers and reduced LES tone seen in night burners who have low LES pressure and therefore greater reflux of gastric contents on lying down. Night burners are known to have longer durations of continuous acid exposure or lowered pH contributing to a greater risk of erosive esophagitis. Increasing LES tone along and improving gastric emptying along with acid suppression are crucial in these patients to prevent development of erosive lesions.[15]

GERD can coexist with delayed gastric emptying wherein there is progressive dilatation of proximal stomach and shortened LES. Hence, greater amounts of solid and liquid materials remains in the stomach after meals and because of its defective emptying, reflux occurs. Not surprisingly, these patients complain more often than those with normal gastric emptying of dyspepsia symptoms like postprandial distension, generalized bloating and abdominal pain, in addition to the usual symptoms of gastroesophageal reflux.[16]

Many GERD patients also suffer from constipation, indicating that they may have reduced motility of the entire GI tract. Symptomatic constipation may be a risk factor not only for the occurrence of GERD, but also refractoriness to PPI monotherapy. In a study refractory factors for PPI therapy in GERD have seen to be high pre-treatment the frequency scale for the symptoms of GERD (FSSG) score, female gender, low body mass index (BMI), low alcohol consumption and symptomatic constipation, the odds ratio being highest in coexisting symptomatic constipation.[17]

PPIs are unstable at a low pH, so retention of PPIs in stomach for a long time may result in impaired acid suppressive effect, so improving transit of the PPI to the upper intestine will be of benefit, which can be aided by adding a prokinetic. Also as some GERD patients refractory to PPI monotherapy have dyspeptic (dysmotility) symptoms, most of them respond to the addition of a prokinetic agent. Adding a prokinetic

agent to the standard dose of PPI is considered more cost-effective than doubling the dose of the PPI in countries like Japan.

Summary Comments from the Panel

- *In past, peptic ulcer was seen more commonly in clinical practice but now GERD is on rise. Bloating and dyspepsia are common complaints along with reflux and regurgitation.*
- *Nocturnal refluxes can be very dangerous. Acid can stay in esophagus for up to 3 hours/180 minutes, which can have serious detrimental effects in supine position contributing to a greater risk of erosive esophagitis. Increasing LES tone, improving gastric emptying along with acid suppression will benefit these patients.*
- *When Psyllium husk (e.g., isabgol) is administered to patients with constipation in GERD, there is increased fecal bulk which further aggravates bloating and acidity symptoms, so use of polyethylene glycol or prokinetic agents to enhance gastric emptying will bring better symptomatic relief from both constipation, dyspeptic and acidic symptoms.*
- Helicobacter pylori *positivity is seen in more than 60% Indian population due to low sanitation and hygiene, but may not be associated with clinically active disease.* H. pylori *testing is recommended in intention to treat (for* H. pylori *eradication) population like patients of gastroduodenal ulcer or FD; however, is not routinely recommended in GERD.*

Gastroparesis: Delayed Gastric Emptying/Constipation

Gastroparesis is a condition of abnormal gastric motility characterized by delayed gastric emptying in the absence of mechanical outlet obstruction. The true prevalence of gastroparesis is unknown; however, it has been estimated that up to 4% of the adult population experiences symptomatic manifestations of this condition.

Constipation may also be associated with gastroparesis. Treatment of constipation with an osmotic laxative has shown to improve dyspeptic symptoms as well as gastric emptying delay. Routine motility testing or gastric scan to confirm gastroparesis by presence of food in stomach at the end of 4 hours are not recommended except if nausea and vomiting persist. Prokinetics may improve predominant symptoms of decreased gastric emptying viz. nausea, vomiting, bloating and constipation.[18]

Summary Comments from the Panel

- *Bristol's stool chart guidelines for IBS in Rome IV can improve diagnosing and categorization.*
- *Good history taking and eliciting patient symptomatology by understanding local and language factors helps in ascertaining right treatment approach and classifying the patient's condition.*
- *Physician's and patient's conception of constipation can differ. Frequency and consistency of stools is not enough alone to judge constipation. Several other factors like time taken for patient to evacuate, incomplete defecation and number of attempts taken to completely evacuate or feel complete evacuation are also determinants.*
- *In diabetic patients, if proper gastric emptying is achieved via prokinetics then even sugar levels (patients who are on oral hypoglycemics) are maintained better or vice versa.*

Depression in FGID

Psychological factors are now accepted to play an important role in many GI symptoms through "gut-brain interactions". In psychiatric tradition, these GI symptoms are often seen as functional symptoms caused by depression. Previous studies have found a high depression level in patients with GI symptoms, and depression is considered an important predictor of FD and IBS. GI symptoms were reported by over 90% major depressive disorder (MDD) patients in one study.

In an outpatient study with IBS and FD in comprehensive hospitals in big cities in China, the prevalence of depressive symptom in FD and IBS were 13.5% and 13.8%, respectively, while less than 12% of depressive subjects had been recognized and treated.[19] The American College of Gastroenterology (ACG) 2017 guidelines recommend use of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitor (SSRIs) in management of DGBI when response to a PPI alone is not satisfactory.[20]

Summary Comments from the Panel

- *DGBIs may be associated with depression which is often underlying, mild and undiagnosed. Treating the same can improve therapy response of GI symptoms also.*
- *TCAs and SSRIs (SSRRIs like escitalopram) can be considered in lack of response to PPIs to address the psychosomatic component of GI problems by mood elevation as well as relaxing gastric fundus to prevent reflux.*
- *However, when seen in real world clinical practice, TCAs/SSRIs are given only to 20% of patients diagnosed with DGBIs while psychiatric referrals are rare, not preferred by either treating physician or patient.*
- *A drug which can address both upper and lower GI motility with an impact on depressive symptoms can be a worthwhile choice of therapy in DGBI.*

An integrated approach to manage DGBIs presenting with upper and lower GI symptomatology with

psychosocial components can involve targeting the appropriate GI receptors, which address the motility of the entire GI tract and syncing the gut-brain axis.

PHARMACOLOGICAL MANAGEMENT OF GI DISORDERS

Review and Comparison of Prokinetic Agents

The clinical data and literature for the 6 commonly prescribed prokinetics in Indian market was reviewed (viz. levosulpiride, acotiamide, itopride, domperidone, cinitapride and mosapride) along with their mechanism of action on upper/lower GI and safety profile and a comparative analysis between levosulpiride and some of these prokinetics (metoclopramide, domperidone, cisapride, itopride) (Table 2).[21-35]

Comparative clinical studies of levosulpiride showed better efficacy than other prokinetics in relieving upper GI symptoms viz. that of regurgitation, vomiting and dyspepsia.[32-35] A small study also showed improved abdominal pain and constipation in patients of IBS.[36]

Levosulpiride can act on multiple levels in DGBI. It acts as a D2 receptor antagonist and a 5-HT4 receptor agonist, therefore it is effective in upper and lower GI symptom relief as well as has action on CTZ. Therefore, levosulpiride can help reduce reflux, vomiting, dyspepsia, bloating and constipation symptoms. Levosulpiride is an atypical neuroleptic, crosses blood-brain barrier and preferentially blocks the presynaptic dopaminergic D2 receptors in brain thereby providing antidepressant effect in the lower doses itself of 50-100 mg. At higher doses, used in psychosis (300 mg or higher), levosulpiride shows antagonism at postsynaptic D2 receptors, which gives rise to neuroleptic action but may also contribute to extrapyramidal side effects.[21-23]

Metoclopramide, another D2 receptor antagonist also crosses blood-brain barrier but does not show atypical dose dependent D2 inhibition, therefore extrapyramidal side effects are present more commonly. Domperidone does not cross blood-brain barrier and being a selective D2 receptor antagonist without 5-HT4 action, it is mainly an upper GI prokinetic and useful in regurgitation, vomiting and dyspeptic symptoms. Domperidone is not recommended for long-term use due to Food and Drug Administration (FDA) cardiac alert.[37]

Itopride acts through cholinergic agonistic and D2 antagonistic pathway and is devoid of 5-HT4 agonism, therefore being effective mainly in upper GI dysmotility.[25-27]

All prokinetics with D2 receptor antagonism are also known to produce galactorrhea and therefore this should be kept in mind, while prescribing in fertile female population.[37]

Acotiamide acts through a cholinergic mechanism and is mainly helpful in postprandial bloating (postprandial distress syndrome [PDS] in patients with dyspepsia) and not in nocturnal reflux, vomiting or constipation.[24]

In three large pivotal randomized controlled trials, prucalopride has been effective in relieving symptoms of chronic constipation and has shown some limited evidence in reducing acid reflux symptoms in chronic constipation patients but larger studies are needed to prove its efficacy in reflux disorders.[38]

Cinitapride, a nonselective 5-HT4 agonist, has shown its efficacy in reflux, dyspepsia and constipation but is known to be associated with increased cardiovascular events in predisposed subjects.[30] Cisapride and tegaserod, both 5-HT4 agonists have been withdrawn for reasons of cardiac safety.[37] Mosapride is now available in Indian market which affects both dyspeptic symptoms and constipation but like other 5-HT4 agonists alone, is devoid of action on the CTZ to suppress nausea/vomiting.[31]

The possible reasons for superior efficacy of levosulpiride cited in literature include both dopaminergic + serotonergic mechanism affecting complete GI motility as well as effect on visceral sensitivity along with synergistic antidepressant activity.

Summary Comments from the Panel

- *In patients who are nonresponsive to initial PPI monotherapy and have symptoms of GI dysmotility, adding a prokinetic agent can be an effective option.*
- *Of all the prokinetic agents currently available in Indian market, levosulpiride outscores in terms of efficacy as seen in various studies, and is the only one which acts at multiple levels of upper and lower GI, the gut-brain axis and CTZ. Caution is advised to follow a strict dosing regimen with regular follow-up, to monitor for rare extrapyramidal side effects. If given in recommended dosage (75 mg/day) for appropriate duration (6-8 weeks), no serious adverse events have been reported in clinical studies.*
- *Metoclopramide crosses the blood-brain barrier causes extrapyramidal symptoms as an adverse effect to a much greater extent when compared with levosulpiride.*
- *Domperidone does not cross blood-brain barrier and is an effective upper GI prokinetic with antinausea/vomiting action also.*

Table 2. Literature Search: Levosulpiride versus Other Prokinetic Agents[32-35]

Drugs compared	Clinical condition	Study design	N	Results	Remarks
Metoclopramide (M) vs. Domperidone (D) vs. Levosulpiride (LS)[32]	Nonulcer FD	Open labeled, RCT - 3 parallel groups: LS 15 mg, D 10 mg and M 10 mg t.i.d. - FD assessed by SF-LFD questionnaire at baseline, 4 wks.	113/120 (38 M, 35 D, 40 LS)	All three therapeutic interventions i.e., LS, D and M effective in improving dyspeptic symptoms - Overall relief rates were significantly higher in the LS group ($p < 0.004$) as compared to D, M group at Week 4.	Dual (dopaminergic + serotonergic mechanism) of LS, effect on visceral sensitivity and synergistic anti-depressant activity was considered for better result.
Levosulpiride (LS) vs. Domperidone (D)[33]	FD	Prospective, double-blind, RCT-Group A: LS 25 mg t.i.d. - 4 weeks, Group B: D 10 mg t.i.d. - 4 weeks. Individual symptoms (abdominal pain, discomfort, nausea, vomiting, anorexia, postprandial bloating, belching, regurgitation, heart burn & abdominal fullness) and severity assessed by 3 point scale at baseline (0), 2, 4 & 8 weeks.	171/182 : 91 each in LS and D group	Highly significant ($p > 0.001$) improvement in symptoms: post-prandial bloating (82%), abdominal pain (81.63%) with LS as compared to D [postprandial bloating (57%), abdominal pain (45%)]. Both groups were comparable for other symptoms.	3 times more nonserious adverse effects observed with LS as compared to D, most common being sedation. Antidepressant activity of LS contributes to increasing gastric motility.
Levosulpiride (LS) vs. Cisapride (C)[34]	FD with delayed gastric emptying	Double-blind 4 weeks RCT - postprandial nausea, vomiting, bloating, belching, abdominal pain, early satiety, anorexia and drowsiness - assessed for severity (VAS), frequency and impact on daily life (4 point scale) - LS (25 mg t.d.s.) and C (10 mg t.d.s.)	30/group	Both C and LS significantly improved ($p < 0.001$) all dyspeptic symptoms. No statistically significant differences in improvement of duration, severity or frequency of overall symptoms. LS was superior to C ($p < 0.05$) in improving symptom impact on QoL. Nausea, vomiting and early satiety showed a significant improvement ($p < 0.01$) in LS, vs. C in severity and frequency.	Both C and LS induced significant ($p < 0.001$) increase in gastric emptying rate, from baseline. No statistically significant difference between the two groups seen. Among patients with no variations in gastric emptying times, symptom scores improved in 78% with LS and 44% with C.
Levosulpiride (LS) vs. Itopride (IT)[35]	GERD	RCT with 3 groups - The control group received rabeprazole and the two test groups received LS and IT. Symptom relief assessed at the end of 2 weeks.	210 - divided in 3 groups	Symptomatic relief and endoscopic recovery, improved QoL is early with LS than IT. LS has lesser side effects (37.2% vs. 73.4%) and better healing outcome (83.6% vs. 54.5%).	Dosage of LS and IT were not standardized.

- *Acotiamide is mainly useful for upper GI symptoms of delayed gastric emptying and bloating.*
- *Itopride mainly has action as an upper GI prokinetic while evidence with prucalopride is mainly for chronic constipation. Mosapride is effective in upper and lower GI symptoms, however, not when vomiting is associated.*
- *D2 receptor antagonists should be used cautiously in fertile female population due to possible occurrence of galactorrhea.*

Place of PPI-Prokinetic Combination in Integrated Management of GI Disorders

PPIs are regarded as first-line agents in management of upper GI disorders like GERD and dyspepsia. However, partial or nonresponse to PPIs has been seen commonly in DGBIs. Various studies on the effect of prokinetics with PPIs as combination therapy were reviewed.[17,39-42]

In a study, high pre-treatment FSSG, acidic and dyspeptic symptom score and presence of constipation suggesting an overall GI dysmotility and were seen to be primary reasons of PPI nonresponse in GERD patients. Such patients showed better symptom relief on adding a prokinetic.[40] Prokinetic addition is seen as a better strategy in countries like Japan than doubling PPI dose in these patients or switching PPIs. Improvement in both acidic and dyspeptic symptoms is seen with adding prokinetics to PPIs, suggesting that improved GI motility improves PPI pharmacokinetics in terms of reaching upper GI for effective absorption and effect. Delayed gastric emptying and slower GI transit increases PPI gastric acid exposure and decreases response. Nausea and vomiting symptoms also respond well with an appropriate prokinetic added to PPI.

Prokinetics increase LES tone, therefore act as a useful add on to PPIs in night burner GERDs to prevent development of erosive esophagitis. Nonacid reflux is also known to be a cause of reflux symptoms where adding a prokinetic would give more benefit than PPI alone in o.d. or b.i.d. dosing.[17] In patients with predominant night reflux symptoms and those who have associated constipation, evening dosing of PPI-prokinetic combination should be considered as an alternative to traditional pre-breakfast dosing. Timing the dose 30-45 minutes before dinner is critical and patient should be explained the same to maintain compliance.

Constipation is seen to worsen reflux, which is further aggravated by adding bulk forming laxatives to therapy, therefore adding a prokinetic to a PPI in such patients can help improve constipation and reflux symptoms. For the same reason adding prokinetic to PPI is also useful in patients of gastroparesis (diabetic or postoperative) who also often have co-existing constipation.

Duration of therapy should be 4-8 weeks for PPI-prokinetic combinations. Prolonged continuous therapy is not recommended. Patients have a tendency to repeat dosing through over-the-counter and repeat purchase so effective patient counseling on the long-term risks and effects of PPI should be imparted. The patient should also be educated on the importance of regular follow-up, strictly adhering to the dose prescribed and timing of taking the dose.

Summary Comments from the Panel

- *It is recommended to add prokinetics to PPIs in following patients:*
  - *Patients having no or partial response to PPI therapy.*
  - *Presence of symptoms of upper and lower GI dysmotility - nausea-vomiting, bloating, postprandial fullness and constipation. A prokinetic with action on all these symptoms acting at various levels of gut-brain axis, is the ideal choice as seen with levosulpiride.*
  - *In GERD patients with predominant nocturnal regurgitation, coexisting dysmotility symptoms, high acidic/dyspeptic symptom scores and coexisting constipation. Adding a prokinetic in these patients can be a more beneficial option than doubling PPI dose or switching PPI.*
  - *In patients with predominant night reflux symptoms and also those with coexisting constipation, pre-dinner dosing of PPI-prokinetic should be considered instead of morning.*
- *Dose and duration of PPI-prokinetic combination use should be well-monitored, and over-the-counter or long-term therapy strictly discouraged. Patient should be well followed up for adverse events.*
- *Prokinetic agents further augment the efficacy of PPIs as they promote faster gastric transit and intestinal absorption of PPIs thereby augmenting PPI response.*

CONCLUSION

It is now accepted and well-recognized that bowel disorders exist as a continuum rather than discreet entities. There is substantial evidence and data available to show that clinically, patients present commonly with significant overlap of upper and lower GI symptoms. There is also a psychosocial component to bowel disorders, which is often under recognized. Therefore, the integrated approach to manage DGBI is the need of the hour.

Appropriate use of prokinetics with PPIs, represents a promising approach to manage these gut-brain disorders. Prokinetics not only provide additional benefit to PPIs by reducing dysmotility or dyspeptic symptoms in the GI tract, but can also improve the gastric transit of PPIs and enhance their effect on relief of acidic symptoms. Prokinetics which exert action at multiple levels of the gut-brain axis through various GI and brain receptors, can give better overall symptomatic relief and thereby improve the quality-of-life of the patients.

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