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Original Article

The Role of Prokinetics on Digestive Tract

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Abstract: The role of prokinetic agents in the management of digestive tract disorders has garnered increasing attention in recent clinical research. This review evaluates the pharmacological mechanisms, efficacy, and clinical applications of prokinetics in gastrointestinal motility disorders, including gastroparesis, functional dyspepsia, and chronic constipation. Prokinetics, which facilitate gastrointestinal peristalsis, do so primarily through interaction with dopamine and serotonin receptors, thereby enhancing gastric emptying and intestinal motility. Various agents, such as metoclopramide, domperidone, and newer medications like prucalopride, are analyzed for their therapeutic profiles, side effects, and patient outcomes. In addition, the review discusses the importance of individualized treatment approaches, taking into consideration the underlying pathophysiology, patient comorbidities, and treatment response variability. The synthesis of current literature indicates that although prokinetics can significantly improve symptoms and quality of life in patients with motility disorders, careful selection of therapy and monitoring for potential adverse effects are crucial. Future directions for research are also highlighted, emphasizing the need for more robust clinical trials to establish the long-term safety and efficacy of these agents in diverse populations. This review aims to provide a comprehensive overview of the evolving role of prokinetics in the management of digestive tract disorders, ultimately enhancing therapeutic outcomes for affected patients.

Keywords: Prokinetic, gastrointestinal motility, serotonin, Macrolide

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Introduction

Prokinetics are pharmacological agents that augment gastrointestinal (GI) contractility, alleviating symptoms in individuals with delayed gastrointestinal motility. Prokinetics have traditionally been utilised to improve gastrointestinal motility and address symptoms associated with motility disorders, such as gastroparesis and constipation. Serotonergic agonists: the substituted benzamide class of prokinetics, with cisapride as the prototype. It promoted the release of acetylcholine from myenteric neurones via a 5-hydroxytryptamine type 4 (5-HT4) receptor-mediated mechanism .(1)
Macrolide antibiotics are the predominant motilin receptor agonists that activate GI motilin receptors, particularly those in the stomach. Erythromycin enhances stomach emptying. It is particularly beneficial in acute gastroparesis, usually within about four weeks following the initiation of therapy, when tachyphylaxis or diminished therapeutic effectiveness may appear. (2)

Prokinetics

Prokinetics are a category of pharmacological agents intended to enhance GI motility, either locally or across the whole digestive tract. These drugs are utilised for several causes, such gastroparesis, aspiration prevention prior to anaesthesia, enhancement of GI performance post-surgery, and improved visualisation prior gastroscopy .(3) They are pharmaceuticals that enhance and synchronize gastrointestinal muscle contractions, facilitating coordination across various segments of the gut and improving the propulsion of intra-luminal contents. Certain prokinetics exert effects in specific regions of the GI tract, while others have a more generalized action corresponding to the locations of their receptor targets among the pharmacological agents .(4)

Here are some additional important aspects and considerations regarding prokinetics that can help deepen your understanding of these medications and their role in gastrointestinal health:

Mechanisms of Action

Prokinetics work by facilitating gastrointestinal motility through various mechanisms including:

- Increasing Contraction Strength: Many prokinetics enhance the contractions of smooth muscle in the gastrointestinal tract, promoting the movement of food. (5)
- Enhancing Coordination: Some agents improve the coordination of contractions between different parts of the GI tract, ensuring efficient transit of contents.
- Modulating Neurotransmitters: Prokinetics often target neurotransmitter systems, such as serotonin and dopamine. (6) For example, certain drugs increase serotonin levels in the gut to promote motility.

Clinical Uses

Prokinetics are utilized to manage a range of GI disorders including:

- Gastroparesis: A condition characterized by delayed gastric emptying, leading to nausea, vomiting, and abdominal discomfort.
- Gastroesophageal Reflux Disease (GERD): By increasing esophageal sphincter tone and gastric emptying, prokinetics can help reduce reflux symptoms.
- Chronic Constipation: In some cases, prokinetics may enhance bowel transit time and relieve constipation. (7)
- Postoperative Ileus: Prokinetics can help restore bowel function after surgery by promoting motility. (8)

Side Effects and Safety

While prokinetics can be beneficial, there are important safety considerations:

- **Dosing and Duration**: Some prokinetics, particularly metoclopramide, carry a risk of side effects such as tardive dyskinesia and should be used at the lowest effective dose for the shortest duration necessary. (9)
- **Contraindications**: Prokinetics are not suitable for everyone. They are contraindicated in patients with certain conditions, such as gastrointestinal obstruction or significant kidney disease. (10)

- **Drug Interactions**: Prokinetics may interact with other medications, which can alter their effectiveness or increase side effects. [11]

Advances and Research

Research continues in the field of prokinetics, exploring:

- New Agents: Ongoing studies aim to discover safer and more effective prokinetic drugs with fewer side effects.
- Mechanisms of Action: Understanding the complex interactions between gut micro biota, gut hormones, and motility may lead to better-targeted therapies.
- Potential Benefits Beyond Motility: Some prokinetic agents are being investigated for their effects on gut health, appetite regulation, and even mood due to the gut-brain axis. [12]

Non-Pharmacological Approaches

Beyond pharmacological options, various lifestyle changes and complementary therapies can support GI motility:

- **Dietary Modifications**: A diet that includes adequate fiber, hydration, and smaller meal portions can enhance digestive motility.
- **Physical Activity**: Regular exercise can stimulate gut motility and improve overall digestive health.
- **Mind-Body Practices**: Techniques such as yoga, meditation, and deep breathing can help manage stress, which may positively influence gut function.

Prokinetics are categorized based on their mechanisms of action, chemical structure, and their specific clinical applications. [13] Below are the main types of prokinetics:

1. **Dopamine Antagonists**:
   - Examples: Metoclopramide, Domperidone
   - Mechanism: These drugs work primarily by blocking dopamine receptors, particularly D2 receptors, in the gastrointestinal tract. This action enhances the release of acetylcholine, leading to increased gastrointestinal motility and improved gastric emptying. Metoclopramide also has central nervous system effects, as it can cross the blood-brain barrier and is sometimes used to treat nausea.
2. **5-HT (Serotonin) Receptor Agonists**:
   - Examples: Prucalopride, Tegaserod
   - Mechanism: These agents target serotonin receptors, particularly 5-HT4 receptors, which stimulate peristalsis in the GI tract. They are often used in the treatment of chronic constipation and have been shown to increase bowel movement frequency.
3. **Motilin Agonists**:
   - Examples: Erythromycin (a macrolide antibiotic at low doses)
   - Mechanism: Motilin is a hormone that stimulates gastric motility. Erythromycin can mimic its effects by acting as a motilin receptor agonist, enhancing gastric emptying and promoting intestinal motility. It is often used for patients with gastroparesis.
4. **Cholinergic Agents**:
   - Examples: Bethanechol
   - Mechanism: These drugs stimulate the parasympathetic nervous system, enhancing cholinergic transmission in the GI tract. This leads to increased smooth muscle contraction and improved gastrointestinal motility.
5. **GABA Receptor Antagonists**:
   - Examples: Various experimental compounds
   - Mechanism: While not yet widely used in clinical practice, some agents target GABA receptors, leading to increased gastrointestinal motility by inhibiting the inhibitory pathways mediated by GABA.
6. **New and Experimental Prokinetics**:
   - Research continues into novel prokinetic agents that may offer advantages over existing therapies. These may include compounds targeting different neurotransmitters or hormonal pathways within the gut to modulate motility.

The role of prokinetics in the digestive tract can be summarized as follows [14]:

1. Enhancing Gastric Motility: Prokinetics promote gastric emptying by increasing the contractions of the stomach muscles. This can be beneficial in conditions such as gastroparesis, where the stomach cannot empty properly.
2. Improving Intestinal Transit: By enhancing bowel motility, prokinetics can help alleviate symptoms of constipation and improve the passage of food through the intestines. This is particularly useful in patients with slow-transit constipation.
3. Reducing Gastroesophageal Reflux Disease (GERD): Prokinetics can help reduce symptoms

of GERD by increasing lower esophageal sphincter tone and promoting gastric emptying, which minimizes reflux and associated heartburn.

4. After Surgery Recovery: In postoperative patients, prokinetics may help restore normal bowel function more quickly, reducing the risk of postoperative ileus (the temporary cessation of bowel function).
5. Management of Functional Gastrointestinal Disorders: Conditions such as functional dyspepsia and irritable bowel syndrome (IBS) can be managed with prokinetics, as they help regulate bowel movements and alleviate discomfort.
6. Symptomatic Relief: Prokinetics can provide symptomatic relief from bloating, nausea, and fullness by promoting more effective digestive processes and reducing the time food spends in the stomach.

Safety and Side Effects

While prokinetics can be effective, they may also have side effects, including:

- Drowsiness or fatigue (especially with metoclopramide)
- Extrapyramidal symptoms (movement disorders) with long-term use of certain agents
- Cardiac arrhythmias (with cisapride, leading to its withdrawal from the market in many countries)

Overall, prokinetics play an important role in the management of various gastrointestinal motility disorders, and their use should be tailored to the individual patient's needs and underlying conditions. [15]

The future role of prokinetics in the digestive tract is likely to evolve significantly as our understanding of gastrointestinal physiology expands, and as new treatment modalities and therapeutic targets emerge. [16] Here are several key areas where prokinetics might play an enhanced role in the future:

1**. Personalized Medicine**

With advancements in genetics and pharmacogenomics, prokinetic therapies may be tailored to individual patients based on their unique genetic makeup and the specific pathophysiological mechanisms underlying their digestive disorders. This personalized approach could improve efficacy and reduce side effects.

2. **Combination Therapies**

Future treatment strategies may involve prokinetics used in combination with other classes of drugs, including antibiotics (for small intestinal bacterial overgrowth), antacids, or other gastrointestinal agents, to provide a multifaceted approach to treating motility disorders and related symptoms.

3. **Novel Prokinetic Agents**

Research is ongoing to develop new prokinetic agents with improved safety profiles and mechanisms of action. Innovative drugs targeting specific pathways in gastrointestinal motility (such as the serotoninergic or dopaminergic systems) could be introduced to the market, offering more options for patients.

4. **Management of Chronic Conditions**

Given the growing recognition of the role of gut motility in conditions such as inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), and functional dyspepsia, prokinetics could become central in managing these chronic conditions, possibly in conjunction with anti-inflammatory or antimicrobial therapies.

5. **Microbiome Interaction**

Emerging research into the gut microbiome may reveal how prokinetic agents influence gut flora and, in turn, how these interactions could be optimized to improve digestive health. Prokinetics may be developed to not only enhance motility but also promote a beneficial microbiome composition.

6. **Use in Neurological Disorders**

As more is understood about the gut-brain axis, prokinetics may be explored in managing gastrointestinal symptoms associated with neurological conditions such as Parkinson's disease, multiple sclerosis, and others. These conditions often involve alterations in GI motility, and effective treatment could improve overall patient quality of life.

7. **Improved Safety Profiles**

Developing new prokinetics that mitigate common side effects (such as movement disorders or cardiac issues) and are safer for

long-term use will be a focal point to enhance patient adherence and broaden their application in clinical practice.

8. **Innovative Delivery Systems**

Research into delivery systems, such as sustained-release formulations or targeted delivery methods, may enhance the effectiveness of prokinetics by ensuring that the drug acts primarily where it's needed, potentially improving therapeutic outcomes

9. **Digital Health Integration**

With the rise of digital health technologies, prokinetics could be integrated into telehealth platforms that monitor symptoms and provide real-time adjustments to treatment plans based on patient feedback, thereby enhancing clinical management of motility disorders.

In summary, the future role of prokinetics in the digestive tract seems promising, with numerous possibilities for refinement, innovation, and improved patient outcomes. As researchers continue to explore the complexities of digestive health, prokinetics may become a cornerstone in the comprehensive management of GI disorders.

To harness the benefits of prokinetics for improving digestive health, it is essential to follow a comprehensive approach that includes understanding your condition, consulting healthcare providers, and possibly adopting lifestyle changes. [17] Here are several steps to help effectively utilize prokinetics:

1. **Consult a Healthcare Provider**

- Diagnosis: Speak with a gastroenterologist or healthcare provider to assess symptoms and receive a proper diagnosis. Conditions such as gastroparesis, functional dyspepsia, or chronic constipation may benefit from prokinetic therapy.
- Medication Management: If deemed appropriate, provider may prescribe prokinetic medications like metoclopramide or domperidone, based on specific needs and health profile.

2. **Follow Prescription Guidelines**

- Adherence to Treatment: Take medications as prescribed, including dosage and timing, to maximize their efficacy.
- Discussions About Side Effects: Maintain an open line of communication with healthcare provider regarding any side effects experienced. They may adjust doses or switch medications based on response.

3. **Lifestyle Modifications**

- Dietary Changes:
  - Incorporate a balanced diet high in fiber to aid bowel function, which can work synergistically with prokinetics.
  - Avoid large meals, high-fat foods, and trigger foods that may exacerbate symptoms.
  - Stay hydrated and include plenty of fluids in your diet.
- Eating Habits:
  - Eat smaller, more frequent meals rather than large ones to prevent overwhelming the stomach, which can help with motility.
  - Chew food thoroughly to facilitate digestion.
- Physical Activity: Regular physical activity can enhance gut motility. Simple activities like walking, yoga, or other forms of exercise can be beneficial.

4. **Monitor Symptoms**

- Keep a Journal: Tracking symptoms and dietary habits can help identify patterns and triggers, allowing for better management of the condition.
- Adjust Treatment Accordingly: Work with healthcare provider to adjust treatment plans as necessary based on symptom tracking.

5. **Be Informed About Alternatives**

- Research complementary therapies that may enhance the effects of prokinetics, such as:
- Probiotics: These can help maintain gut health and may work in conjunction with prokinetics.
- Digestive Enzymes: They may help in digestion and nutrient absorption.
- Herbal Remedies: Some patients find relief using herbal treatments, but consult provider before starting any new therapies.

6. **Regular Follow-ups**

- Schedule regular check-ups with healthcare provider to monitor progress, adjust treatment as needed, and re-evaluate the condition.

7. **Education and Support**
   - Educate patients about condition and potential treatments. Joining support groups or forums may provide additional insights and motivation from others who have similar experiences.

8. **Long-Term Management**
   - Consider that prokinetics may be part of a long-term management plan rather than a one-time fix. Regular evaluations to understand their impact and any need for adjustments are vital for sustained benefits.

By following these steps, we can maximize the benefits of prokinetics for digestive health while ensuring a comprehensive approach to managing any underlying conditions. Always prioritize open communication with healthcare professionals to tailor treatment plan effectively.

Overcoming the side effects of prokinetics while still benefiting from their digestive tract roles largely depends on effective communication with healthcare provider, lifestyle adjustments, and proactive management strategies. Here are some practical approaches to managing side effects associated with prokinetic medications [18]:

1. **Consult Healthcare Provider**
   - Discuss Side Effects: If experience side effects, such as drowsiness, fatigue, or movement disorders, communicate these concerns to healthcare provider. They may adjust dosages, switch medications, or suggest alternatives.
   - Regular Monitoring: Schedule regular follow-up appointments to track symptoms and the effectiveness of treatment.

2. **Manage Drowsiness and Fatigue**
   - Timing of Dose: If you experience drowsiness, taking medication at bedtime or during periods when can rest may help minimize daytime sleepiness.
   - Caffeine: Moderate caffeine intake (if appropriate) may help counteract drowsiness, but consult doctor about its suitability for condition.

3. **Address Gastrointestinal Discomfort**
   - Prokinetics can sometimes lead to gastrointestinal symptoms like cramping or diarrhea. Here's how to manage those:
   - Start with Low Doses: If starting a new prokinetic, it's possible to begin with a lower dosage and gradually increase it as tolerated.
   - Diet Modifications: Adjust diet to include bland, easy-to-digest foods if it is experience discomfort, and gradually introduce fiber or other dietary changes to find what works best for patients.

4. **Prevent Extrapyramidal Symptoms**
   - Stay Informed: Awareness of the signs of movement disorders, and immediately report any unusual symptoms (such as shaking or involuntary movements) .
   - Consider Alternatives: If extrapyramidal symptoms develop, provider may switch patients to a different class of prokinetics that has a lower risk for these side effects.

5. **Stay Hydrated**
   - Ensuring proper hydration can help minimize gastrointestinal side effects like constipation or diarrhea. Aim to drink plenty of fluids throughout the day.

6. **Implement Lifestyle Changes**
   - Regular Exercise: Engaging in regular physical activity can improve overall digestive health and may help alleviate some side effects related to gastrointestinal motility.
   - Stress Management: Practices such as yoga, mindfulness, or breathing exercises can help reduce stress, which may exacerbate digestive symptoms.

7. **Consider Probiotics**
   - Discussion with the provider the possibility of incorporating probiotics into regimen. Probiotics can enhance gut flora balance and may help counteract diarrhea or gastrointestinal discomfort.

8. **Adjust Meal Timing and Size**
   - Eating smaller, more frequent meals can help reduce the burden on the digestive system and may alleviate side effects like nausea or cramping.

9. **Monitor Symptoms**

- Keep a journal of side effects alongside any other symptoms. This will help to track potential triggers, manage them effectively, and adjust treatment accordingly.

10. **Utilize Support Systems**

- Engaging in support groups or communities where patients share their experiences and coping strategies can provide additional insights and motivation.

Prokinetics can be an effective tool for managing gastrointestinal motility disorders, but potential side effects need to be carefully managed. By working closely with healthcare provider, making informed lifestyle choices, and employing proactive strategies, can enhance the benefits of prokinetics while minimizing adverse effects. Always prioritize open communication and tailored approaches based on individual response to treatment.

The following are the main prokinetic agents used nowadays which discussed in details:

Serotonin

Serotonin (5-HT) influences motility of the intestine in humans; nevertheless, preliminary research indicated that it enhances small intestine motility while inhibiting stomach and colonic phasic contractions. [19] Sigmoid colonic motility seems to increase in individuals with IBS. The impact of 5-HT in the dysmotility associated with IBS is ambiguous, while evidence suggests a potential correlation between endogenous levels of 5-HT and motility of the sigmoid colon reported in both IBS patients and healthy subjects.

Strong associations were seen between the fed sigmoid colonic motor activity index and platelet-depleted plasma 5-HT levels in both IBS individuals and healthy subjects; the R values indicate that the 5-HT level accounts for a maximum of 20% of the variation in postprandial motility of the colon .[20] Nonetheless, further human data indicate the involvement of 5-HT pathways in motility of the colon under pathological conditions and in pharmacological models. Carcinoid diarrhoea, which is linked to elevated endogenous 5-HT levels, is characterised by increased intestinal tone, especially after meals. Secondly, the 5-HT4 agonists as tegaserod, it enhances phasic contractility and colonic tone. Third, 5-HT3 antagonists impede the elevation of colonic tone postprandially in both healthy individuals as well as individuals with carcinoid diarrhea. [21]

Serotonin induces secretion; carcinoid diarrhoea exemplifies secretory diarrhoea. The secretory actions of serotonin are facilitated by several receptors: 5-HT stimulates secretion in the human ileal mucosa through a 5-HT4 receptor, whereas a 5-HT2A receptor seems to mediate the action in the sigmoid colon of humans. [22]

Macrolides

Macrolides are mostly bacteriostatic. Bactericidal properties might manifest under certain circumstances or against certain microbes. They reversibly attach to the 23S ribosomal RNA (rRNA) inside the 50S subunit of sensitive species, therefore obstructing mRNA-directed protein synthesis. Furthermore, they promote the dissociation of peptidyl-tRNA throughout translocation, limiting RNA-dependent protein synthesis and bacterial proliferation**.** [23]

The GI tract discomfort, characterised by abdominal cramps, vomiting, nausea, and diarrhoea, is often linked to the consumption of macrolides. [24]

The mechanism responsible for these impacts remained unidentified until the mid-1980s, when two groups separately presented evidence of erythromycin's GI prokinetic impact .[25] Erythromycin emulates the action of motilin on the GI system. [26]

Mechanism of Action:

1. Motilin Receptor Agonism:
   - Erythromycin acts as a motilin receptor agonist. Motilin is a hormone that stimulates smooth muscle contractions in the gastrointestinal tract [26], particularly in the stomach and duodenum. By mimicking the action of motilin, erythromycin enhances gastric motility and promotes the coordinated contractions required for effective digestion and propulsion of food through the GI tract.
2. Electrophysiological Effects:

- In addition to its hormonal action, erythromycin influences gastrointestinal smooth muscle through various electrophysiological mechanisms. It can enhance the influx of calcium ions into smooth muscle cells, thereby increasing contractility.

Clinical Applications:

1. Gastroparesis:
   - Erythromycin is often used off-label to treat gastroparesis, a condition characterized by delayed gastric emptying, which can lead to symptoms such as nausea, vomiting, and bloating. The prokinetic effect of erythromycin helps in accelerating gastric emptying and improving symptoms of this condition.
2. Post-operative Ileus:
   - Erythromycin has also shown promise in reducing the duration of post-operative ileus—a temporary cessation of bowel function that can occur after abdominal surgery. By stimulating GI motility, it can assist in the resumption of normal bowel function.
3. Other Gastrointestinal Disorders:
   - It may be utilized in certain cases of functional dyspepsia and chronic constipation, especially when motility issues are suspected to be a contributing factor.

Advantages:

- Rapid Onset of Action: Erythromycin has a relatively quick onset of action, often producing results within minutes to hours, making it effective for acute symptoms related to motility disorders.
- Dual Functionality: While providing prokinetic effects, erythromycin also serves as an antibiotic, which may benefit certain patients with underlying infections that require treatment.

Limitations and Side Effects:

1. Side Effects:
   - Common side effects include gastrointestinal discomfort, such as abdominal pain and diarrhea. Long-term use may lead to antibiotic resistance or impact gut microbiota.
2. Tolerance:
   - Patients may develop tolerance to the prokinetic effects of erythromycin over time, necessitating higher doses or alternative treatments.
3. Drug Interactions:
   - Erythromycin can interact with various medications, affecting drug metabolism due to its inhibitory effect on cytochrome P450 enzymes, which requires careful consideration in polypharmacy scenarios.

Development of motilides

The study on the potent gastrokinetic impact of erythromycin was received with much excitement. The unexpected impact of erythromycin is attributed to its function as an agonist of motilin receptors, leading to the development of various motilides, such as ABT-229, which possess no antibacterial properties. The results of clinical studies including ABT-229 were distinctly unsatisfactory for symptom amelioration. A comprehensive double-blind placebo-controlled trial including 612 individuals suffering from functional dyspepsia, who were allocated to receive either a placebo or doses of 1.25, 2.5, 5.0, or 10 mg of ABT-229, revealed no improvement in symptoms. Conversely, an inverse dose-response was seen for postprandial fullness, and ABT-229 seemingly inhibited the advantageous impact of placebo**.** [27]

In this condition of GI tract, Talley et al. report that a research including 270 individuals with diabetes mellitus, designed similarly, resulted in unfavourable effects and exacerbated dyspeptic symptoms. [27]

The authors concluded that motilides are ineffective for managing gastroparesis and that accelerating stomach emptying isn't an appropriate treatment objective. These findings are extensive and may lack justification. Multiple variables might have influenced the adverse results of both investigations.

Relevance of ABT-229 pharmacology:

The authors presume that the prokinetic action remained intact throughout the phase II trials, despite the absence of repeated measurements of stomach rate of emptying at the conclusion of the period of therapy. The research strongly suggests

that ABT-229 may diminish in efficacy with extended therapy. In animal research, a one-month therapy with ABT-229 resulted in full tachyphylaxis to both ABT-229 and motilin, perhaps due to significant down-regulation of the motilin receptors.

The half-life of ABT-229 in plasma is estimated at 20 hours, perhaps contributing to the downregulation of receptors. Research with 9 healthy subjects assessed the impact of 4 mg and 16 mg dosages on GI motility and stomach emptying after two successive meals. This investigation validated the impact on the evacuation of the first meal; however, the evacuation of a subsequent similar meal consumed 4 hours later remained unaffected. The amplitude and frequency of antral contractions improved following the first meal, but not following the 2nd meal. Nonetheless, after the 2nd meal, plasma concentrations of ABT-229 remained increased without any prokinetic impact, so verifying the occurrence of tachyphylaxis. Tachyphylaxis presents a genuine issue and might have taken part in the lack of treatment response following 4 weeks of therapy, however this doesn't account for the deterioration compared to placebo. [28]

Relevance of other pathophysiological mechanisms

Further evidence has been shown that functional dyspepsia is a diverse condition characterised by distinct underlying pathophysiological abnormalities linked to unique symptom patterns. Delayed stomach emptying, seen in up to 33% of individuals, is linked to postprandial nausea, fullness, and vomiting. Impaired stomach adaption to a meal occurs in 40% of individuals and is linked to early satiety and loss of weight. Hypersensitivity to stomach distention, present in 35% of patients, correlates with manifestations of epigastric discomfort, frequent belching, and weight loss. Diabetic individuals have also shown impaired accommodation and heightened sensitivity to stomach distention. Several findings indicate that motilide prokinetics may negatively impact gastric accommodation to a meal and susceptibility to gastric distension .[29]

The use of erythromycin significantly enhances tone and phasic contractile activities in the proximal stomach. Phasic and tonic contractions both result in heightened active wall tension in the proximal stomach, which is essential for gastric mechanosensitivity. In healthy individuals, there are noticeable proximal stomach phasic contractions that occur spontaneously.

Erythromycin enhances the severity and frequency of these contractions, leading to a substantial rise in felt contractions. While administering erythromycin, participants exhibited markedly elevated perception ratings at the same distending volumes or pressures, so simulating hypersensitivity to stomach distension. The use of motilin or erythromycin diminishes meal-induced relaxation of the proximal stomach, so simulating decreased accommodation to a meal. While precise data for ABT-229 are lacking, it is plausible that both pathways taken part in the exacerbation of dyspeptic symptoms throughout therapy. [28]

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