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New developments in the treatment of gastroparesis and functional dyspepsia

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Functional dyspepsia (FD) and gastroparesis are frequent causes of upper gastrointestinal symptoms such as postprandial fullness, early satiation, epigastric pain or burning, upper abdominal bloating, bothersome belching, nausea and vomiting. The underlying pathophysiological mechanisms are heterogeneous and involved mechanisms such as abnormal gastric motility (accommodation, emptying), visceral hypersensitivity, low grade mucosal inflammation and cellular changes in enteric nerves, muscle or interstitial cells of Cajal. Patient-reported outcomes for evaluating treatment efficacy in these conditions were recently developed and validated. Prokinetic agents, which enhance gastric motility, are used for treating both gastroparesis and FD. In FD, besides acid suppressive therapy and *Helicobacter pylori* eradication, neuromodulators and drugs that enhance gastric accommodation can be applied. In gastroparesis, anti-emetics may also provide symptom relief. Novel approaches under evaluation in these conditions are the fundus relaxing agents acotiamide and buspirone and the antidepressant mirtazapine in FD. For gastroparesis, recently studied agents include the prokinetic ghrelin agonist relamorelin, the prokinetic serotonergic agents velusetrag and prucalopride, the anti-emetic aprepitant and per-endoscopic pyloric myotomy procedures.

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Introduction

Functional and motility disorders of the stomach are commonly encountered in gastroenterology clinical practice [1•,2]. Patients present with upper gastrointestinal symptoms such as postprandial fullness, early satiation, epigastric pain or burning, upper abdominal bloating, bothersome belching, nausea and vomiting, and routine diagnostic work-up for underlying structural or metabolic disease, such as endoscopy, blood tests and radiological examination often fail to identify a cause for the symptoms.

Functional dyspepsia (FD) is considered a heterogeneous condition: postprandial distress syndrome (PDS), characterized by meal-related symptoms such as postprandial fullness and early satiation, and epigastric pain syndrome (EPS), characterized by meal-unrelated symptoms such as epigastric pain or burning [1•,2].

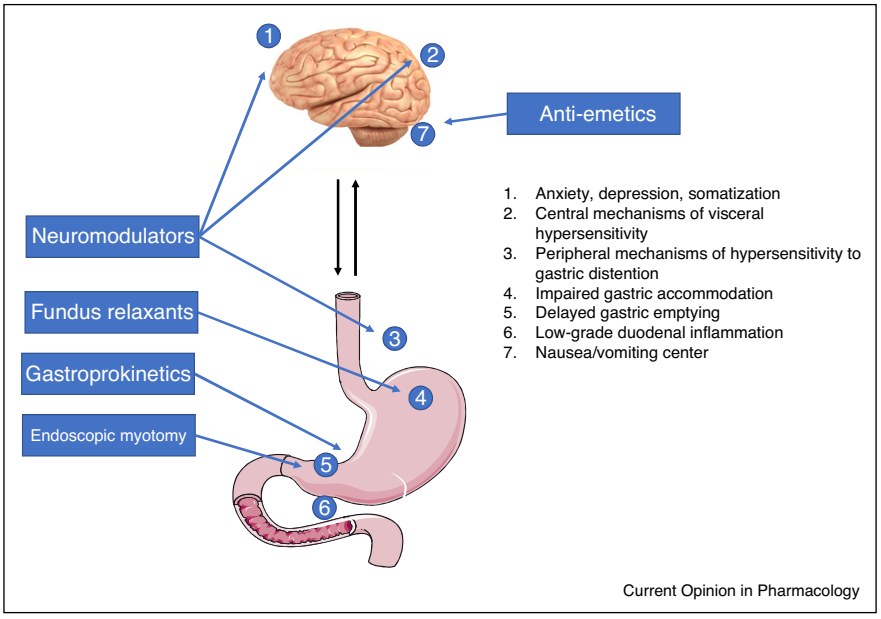
In patients with persisting symptoms, assessment of motility is often the next step, most commonly measurement of gastric emptying. When this is delayed, the patient is considered as having gastroparesis, a syndrome characterized by upper gastrointestinal symptoms including nausea or vomiting, and delayed gastric emptying in the absence of mechanical obstruction [3,4]. Gastroparesis occurs in several clinical settings, particularly as a complication of diabetes mellitus, upper gastrointestinal surgery, neurological disease, collagen vascular disorders, viral infections, drugs, *etc.* In the majority of cases no underlying cause is found and gastroparesis is termed idiopathic [3,4]. This review summarizes current pathophysiological concepts and recent progress in the treatment of functional dyspepsia and gastroparesis.

Pathophysiological concepts: disordered motility, visceral hypersensitivity and mucosal alterations

Pathophysiological mechanisms in FD

The pathophysiology of FD is most likely heterogeneous, with different underlying mechanisms contributing to somewhat more specific diverse symptom patterns [1•,2] (Figure 1). Impaired gastric accommodation to a meal, delayed gastric emptying and hypersensitivity to gastric distention are the mechanisms classically implicated in PDS [5]. Impaired gastric accommodation to a meal is present in up to 50% of FD patients, is associated with early satiation and weight loss, and may result in redistribution of the meal to the distal stomach and more rapid gastric emptying [5,6•]. Visceral hypersensitivity is present in approximately one third of FD patients and is associated with higher intensity ratings of all epigastric symptoms, including pain [5,7•]. Visceral hypersensitivity is supported by functional brain imaging studies or lack of anti-nociceptive in response to gastric signals and by co-morbid psychosocial disorders such as anxiety, depression

Figure 1



Pathophysiological mechanisms serving as (potential) therapeutic targets in functional dyspepsia and gastroparesis.

and somatization [8,9•,10]. Delayed gastric emptying occurs in up to one third of FD patients and, in some series, has been associated with postprandial fullness, nausea and vomiting [4,5,11].

More recently, impaired duodenal mucosal integrity, with low-grade mucosal inflammation characterized by eosinophils and mast cells, has been reported as a putative pathophysiological mechanism in FD [1•,5,12,13], conceivably associated with changes in upper gastrointestinal microbiota [14,15].

Mechanisms in gastroparesis

Cellular mechanisms

Several studies have documented loss of interstitial cells of Cajal (ICC) and fibrosis of the muscular layers in severe cases of diabetic gastroparesis [16,17]. Similar findings have been reported in idiopathic gastroparesis patients, but inflammatory cell infiltration around myenteric neurons and neuronal loss have also been implicated [16,17]. The triggers leading to ICC or neuronal loss are incompletely understood. Animal models of type 1 diabetes have implicated a phenotypical switch from anti-inflammatory or alternatively activated M2 macrophages to pro-inflammatory M1 or classically activated macrophages [18]. While some human observations are consistent with such a mechanism [19], other data from patients with idiopathic gastroparesis do not support the reduction in ICCs or M2 macrophages, and in contrast provided evidence of reduced electrically-coupled fibroblast like cells that are positive for PDGFRα with no reduction in M2 macrophages [20].

Pathophysiology

In diabetic and idiopathic gastroparesis, the correlation of symptoms with the delay in gastric emptying is the subject of continuing debate, with recent analysis showing the best correlations are found in studies that use optimally measured gastric emptying for at least 3 hours by scintigraphy or breath test [21]. Similar to FD, mechanisms such as impaired accommodation and visceral hypersensitivity also contribute in patients with gastroparesis [22,23].

Diagnostic considerations in patients with upper GI symptoms

Gastroparesis may result from ***iatrogenic causes***, including bariatric and other gastric surgery and, more commonly, from medications. The two most relevant drug classes are all opioids and anti-diabetic medications such as pramlintide and GLP-1 agonists (e.g. exenatide and liraglutide), but not dipeptidyl peptidase IV inhibitors such as vildagliptin and sitagliptin.

After excluding obstruction or significant mucosal diseases, ***getting the right diagnosis*** for the patient's symptoms is an essential first step, especially because classical symptoms of gastroparesis may result from impaired gastric accommodation. Among 1287 patients presenting to a tertiary care center with upper gastrointestinal symptoms, there was an approximately equal proportion (~25%) with delayed gastric emptying, impaired gastric accommodation, a combination of both, or absence of both [6•]. This is consistent with a broader spectrum of gastric neuromuscular dysfunctions that may present with