Drug Treatments for Gastroparesis—Why Is the Cupboard So Bare?

See "Efficacy and Safety of Drugs for Gastroparesis: Systematic Review and Network Meta-analysis," by Ingrosso MR, Camilleri M, Tack J, et al, on page 000

While, for many understandable reasons, the true prevalence of gastroparesis in the community has not been accurately defined, there is little doubt that patients who attend our clinics, emergency departments, and hospitals carrying this diagnosis are severely impacted and that their illness incurs significant costs for the individual, health care systems, and society at large.[1,2] A critical and comprehensive assessment of the pharmacotherapeutic landscape relating to gastroparesis is, therefore, most welcome and will be eagerly anticipated by practitioners.

Using a network analysis that permits comparisons between treatments which (for the most part) have not been compared head-to-head, Ingrosso et al[3] provide a league table of the relative efficacy of available drugs. This approach is especially applicable to the topic of gastroparesis, where studies comparing active agents have been rare and protocols have varied. What emerges is depressing and discouraging and suggests that we have made scant progress in the development of effective therapies for this condition.

Although not quite in the era of William Withering and the foxglove, the drugs that emerge with a modicum of positivity (more faint praise than blue riband) are relatively ancient and burdened by issues with availability and adverse events. The only one currently available in the United States and indicated for gastroparesis, metoclopramide, dates back to 1964![4,5] Why such lack of progress and why do the league tables produced by this excellent research documenting the relative efficacy of these drugs look more Sunday amateur league than Premier Division? There are several problems.

Central to all that ails gastroparesis is the entity itself. Intrinsic to its definition, the presence of a constellation of symptoms in an individual with a demonstrated delay of gastric emptying, and in the absence of any mechanical impediment to the evacuation of the stomach,[3,6] implies that these symptoms are coherent and specific and that there is standardization in the performance and interpretation of gastric emptying studies. Neither is the case. The spectrum of symptoms now linked to gastroparesis has been extended well beyond the expected nausea, vomiting, early satiety, and postprandial fullness to include upper abdominal pain and bloating[3,6,7]; an extension that risks overlap with functional dyspepsia[8] and irritable bowel syndrome and greatly complicates strategies based on stimulating motility or suppressing nausea and vomiting. To complicate matters further, it has also been reported, first, that symptom patterns and impact are little influenced by the presence or absence of gastric emptying delay among individuals with chronic nausea and vomiting[9] and, second, that overlap between functional dyspepsia and gastroparesis is considerable, with patients moving back and forth between these diagnoses over time.[8]

Mindful, perhaps, of these issues and aware of the limitations of the available literature, Ingrosso et al[3] nimbly skirted around this minefield by accepting not only those with a documented delay in emptying but also those with symptoms compatible with gastroparesis. They were equally liberal in their definition of gastric emptying delay, accepting results from radiographic, radionuclide, isotope breath testing, or wireless motility capsule studies and regardless of study protocol or interpretation.

Although this may have provided a more "real-world" representation of the patients who are seen in our clinics, it undoubtedly generated a study population that encompassed a broad swath of clinical expression extending from functional dyspepsia to end-stage gastroparesis. This approach also clings to the label that will remain with these patients forever and may doom them to increasingly invasive and, perhaps, inappropriate procedures: gastroparesis.

I tend to abide by the recommendation proposed by Masaoka and Tack[10] some years ago that one should use the term gastroparesis only "when persistently and severely delayed gastric emptying is found in the absence of mechanical obstruction." Instead, studies of drug therapy in gastroparesis have come to be populated by a heterogeneous mix of individuals of varying underlying etiology, symptom profile, and disease severity. Hardly a level and inviting testing ground for any new intervention.

An obsession with gastroparesis as the basic issue among patients with "gastroparesis-like" symptoms has translated into a therapeutic fixation on the acceleration of gastric emptying. This too has led to frustration and disappointment. As already mentioned, symptoms are a poor predictor of the rate of gastric emptying, and a normalization of delayed emptying has not consistently correlated with symptom responses and vice versa.[11,12] Oblivious to research illustrating how upper gastrointestinal symptoms can result from several other derangements in foregut physiology, such as impaired accommodation of the upper stomach, visceral hypersensitivity, and antropyloric distensibility and dysmotility,[13–16] efforts in drug discovery have been concentrated on developing the next prokinetic. Disappointment was not surprising, and given the basic pharmacology of many of the drug classes tested, some degree of dangerous flirtation with cardiac and neuropsychiatric adverse effects inevitable.

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EDITORIAL

This work by Ingrosso et al[3] has assembled a literature of variable quality and summarized it for us in a high-quality systematic review and network analysis. That the outcome disappoints is not their fault but a consequence of valiant but doomed efforts to treat the undefinable with agents chosen on assumptions that are largely unsupported. Almost 30 years ago, Crean et al[17] described dyspepsia as "a disease space of undetermined dimensions occupied by many conditions that share a more or less common core of symptoms, some of which may coexist and like others we find it difficult to define." This could equally well describe gastroparesis as we now know it.

So how do we escape from this morass? We need to know what we are dealing with and what generates these symptoms before we attempt to develop new drugs. Studies from the National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases Gastroparesis Clinical Research Consortium have provided detailed descriptions of the characteristics of this population,[18] which should foster an appreciation of the challenges ahead. Innovative translational work reveals glimpses of new pathophysiological factors and may, thereby, open novel therapeutic avenues.[19,20]

Meanwhile, we can strive to alleviate symptoms with what appears effective and available. Metoclopramide, one of the winners in the meta-analysis, is an effective antiemetic and prokinetic, although its use should be tempered by the possibility of extrapyramidal adverse effects. Ondansetron, promethazine, dronabinol, aprepitant, and related compounds can be used to allay nausea and vomiting. If compromised, hydration and nutrition will need to supported. As more data accumulates, we look forward to clarity on the roles of more invasive options, such as gastric electrical stimulation and pyloromyotomy. On the basis of the work of the National Institute of Diabetes and Digestive and Kidney Diseases consortium, we are now in a position to better understand the clinical challenge, delineate coherent subgroups, and define therapeutic objectives. Accordingly, we can look forward to defining predictors of response so that an individualized approach to care can emerge.

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The author discloses no conflicts. Q4

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