Making the stomach pump better: the answer for gastroparesis?

Comment on:

Vijayvargiya et al, "Effects of Promotility Agents on Gastric Emptying and Symptoms: a Systematic Review and Meta-Analysis" *Gastroenterology (*in press)

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"Everything should be made as simple as possible, but not simpler"

Albert Einstein

Gastroparesis, defined by abnormally slow gastric emptying in the absence of mechanical obstruction[1], affects up to 1.8% of the population, with most undiagnosed[2], and hospital admissions for gastroparesis have quadrupled in the last 1-2 decades[3]. Increased recognition of the disorder reflects the development of techniques to quantify gastric emptying[4]. Gastroparesis is associated with symptoms such as nausea, vomiting, and abdominal pain, and can impair absorption of nutrients and oral medications[1]. In type 1 and insulin-treated type 2 diabetes – which underlies about one third of gastroparesis cases – the unpredictability of carbohydrate absorption may cause a mismatch with the action of exogenous insulin, leading to increased glycemic variability and propensity to hypoglycemia[5]. Management of gastroparesis is suboptimal and there is a need for new therapies[6], ideally with the goal – as in other areas of medicine – of personalized management.

For a disorder characterized by delayed gastric emptying, the solution appears intuitively simple: identify interventions that accelerate emptying. While most patients are prescribed prokinetic medication, systematic reviews have hitherto concluded that, while these drugs accelerate gastric emptying and improve symptoms, there is no relationship between these two outcomes[7, 8]. However, such analyses were beset by heterogeneity in clinical trial design, type and duration of prokinetic therapy, and methodology used to evaluate gastric emptying and symptoms. In this issue of *Gastroenterology*, Vijayvargiya and colleagues report the outcomes of their systematic review of prokinetic drugs[9]. Of 899 studies involving

patients with gastroparesis or functional dyspepsia, 67 were included in the systematic review, and 31 in a meta-analysis limited to randomized trials. Of the latter, 14 evaluated both gastric emptying and symptoms. Despite differing methodologies for quantifying gastric emptying, including ultrasound and MRI, as well as the more standard scintigraphic and breath tests, data were included if reported as a gastric half-emptying time (t1/2). Symptoms were scored by diverse questionnaires, so their meta-analysis presented a challenge, overcome by calculating standardized mean differences of composite symptom scores. The authors found that gastric emptying was accelerated (mean change in t1/2 -16.3 min, 95%CI -22.1 to -10.6 min), and symptoms reduced (mean change -0.25 standard deviations (SD), 95%CI -0.37 to -0.13 SD) in all studies. While meta-regression found no relationship between improvement in symptoms and gastric emptying, a significant relationship emerged when 5 studies deemed to have used "suboptimal" gastric emptying methodology were excluded. The investigators, accordingly, concluded that identifying drugs that accelerate gastric emptying should represent a focus in the development of new therapies.

Limiting the analysis to randomized trials is a strength of this meta-analysis; open label studies in gastroparesis often indicate overly promising benefits[8], and should be viewed circumspectly. A limitation, however, is that the motilides – one of the most potent prokinetic classes when given acutely – were excluded, because they appear susceptible to tachyphylaxis, a suggested (albeit unproven) reason for the failure of ABT-229 and mitemcinal in clinical trials[10]. However, all drugs included in the meta-analysis have mechanisms for symptom relief unrelated to their prokinetic effects: D_2 antagonists have central antiemetic properties; ghrelin agonists may enhance appetite and reduce nausea by

acting on the vagus nerve[11]; and the $5HT_4$ agonist, cisapride, is also (like metoclopramide and domperidone) a weak $5HT_3$ antagonist. Over 50% of the studies involved cisapride, which is no longer routinely available due to the risk of cardiac arrhythmias. Newer (and safer) $5HT_4$ agonists, eg. prucalopride and velusetrag, developed to treat constipation, may have useful prokinetic effects in gastroparesis[12] but were not represented. A further limitation is that treatment duration was <1 month in >50% of studies, and many involved only single doses, although the authors report that neither gastric emptying nor symptom outcomes were related to duration of therapy. Finally, the basis for classifying some gastric emptying methodologies as suboptimal is debatable. The low-fat 255kcal test meal (egg white with bread and jam) recommended by the American Neurogastroenterology and Motility Society/Society of Nuclear Medicine[4] has strengths and limitations. While there is clear evidence that patients should be studied for at least 2 hours after the test meal[13], there is not uniform agreement that only emptying of solids is relevant; we believe that both solid and nutrient liquid emptying should ideally be measured concurrently using 2 isotopes, since the results are frequently discordant[14].

The outcome of this[9] and other analyses[7, 8] attest to the hetergeneous etiology of symptoms in gastroparesis (**Figure**) which has major implications for management. That the relationship between symptom improvement and acceleration of gastric emptying is weak is not surprising. Many patients with diabetes and delayed gastric emptying have few or no gastrointestinal symptoms, while those with prominent symptoms may have normal, or abnormally rapid, emptying[14]. A similar disconnect between symptoms and gastric emptying has been observed in functional dyspepsia[15]. Diverse abnormalities including impaired accommodation of the proximal stomach, hypersensitivity to gastric distension or small

intestinal nutrients, disturbances of the gastric electrical rhythm, afferent nerve dysfunction, and central processing of gut sensations may all contribute to symptoms[16]. Moreover, gastroparesis is associated with a high prevalence of both small intestinal dysmotility[17] and gastroesophageal reflux[18]. Importantly, prokinetic therapies may have disparate effects on these elements, eg. motilides impair gastric accommodation while cisapride improves it[19], and the $5HT_{1A}$ agonist, buspirone, may enhance accommodation and improve postprandial symptoms, but does not alter gastric emptying[20]. Characterizing the relevant motor and sensory dysfunctions may be the key to achieving effective personalized management.

In trials of novel medications in patients with symptomatic gastroparesis, FDA guidance that patient-reported outcomes should be the primary endpoint is sound, and the tools for achieving this using variants of the Gastroparesis Cardinal Symptom Index are now the standard[6]. Measurement of gastric emptying using a precise technique such as scintigraphy, which remains the "gold standard", nonetheless provides important mechanistic information when considering effects on nutrient absorption, postprandial glycemic responses in diabetes, or potential tachyphylaxis. However, gastric emptying represents but one of a number of facets of normal and disordered gastro-duodenal physiology, and its relationship to symptoms should not be over-simplified.

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Figure legend

Potential mechanisms contributing to upper gastrointestinal symptoms

In addition to delayed gastric emptying (1), several mechanisms may contribute to the generation of upper gastrointestinal symptoms in functional dyspepsia or gastroparesis, including hypersensitivity to gastric distension (2) or small intestinal nutrient and chemical stimuli (3), impaired gastric accommodation (4), esophageal (5) and small intestinal (6) dysmotility, abnormal gastric electrical rhythms (7), vagal afferent nerve dysfunction (8), or disordered central processing of gastrointestinal afferent signals (9).