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Botulinum Toxin Injection for Treatment of Gastroparesis

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Introduction

Refractory gastroparesis is a challenging disorder characterized by symptoms of nausea, vomiting, early satiety, post-prandial fullness and abdominal pain for which viable effective treatment options are scarce.^{1, 2} Although the cause of most cases remains idiopathic, gastroparesis has known associations with diabetes mellitus and with prior surgery. Clinicians will likely continue to see a rise in gastroparesis as the incidence of the metabolic syndrome increases worldwide. One relatively safe intervention, injection of botulinum toxin (BoNT) in the pylorus, has been controversial but still widely practiced. In this article we will review pyloric dysfunction in gastroparesis, botulinum toxin as a therapeutic modality and its potential use in gastroparesis based on the latest literature.

Pyloric dysfunction in gastroparesis

When Mearin and colleagues first described pyloric dysfunction in diabetic gastroparesis in 1986,³ the pathogenesis and pathophysiology of the disease was poorly understood (it arguably remains so today). Historical studies had demonstrated a link between delayed gastric emptying and diabetes and early therapeutic approaches consisted of “prokinetic” agents such as with domperidone or metoclopramide.⁴⁻⁸ These drugs seemed initially promising, but rarely provided long-term “curative” solutions for patients suffering from clinical gastroparesis. Given a pathognomonic lack of mechanical obstruction in these

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patients, it was hypothesized that pyloric dysfunction may be a component of their overall upper gut dysmotility, contributing to symptoms of nausea and early satiety by impeding gastric emptying. In their landmark study of 24 diabetic patients with symptoms consistent with gastroparesis, Mearin and colleagues identified periods of unusually prolonged and intense tonic pyloric contractions, or “pylorospasms,” via endoscopic manometry,³ forming the basis of an emerging hypothesis that the pylorus is a potential therapeutic target in gastroparesis.

However, manometry has several limitations. While it measures static pressure exerted over an area of surrounding tissue, it cannot quantify radial force nor can it distinguish between relaxed and contracted state.⁹ Newer technologies such as the endoFLIP may overcome these issues, as first suggested by McMahon and Gregerson in 2007.¹⁰ Two studies have investigated the pyloric sphincter using this technique. The first study noted decreased pyloric compliance in patients with gastroparesis compared to healthy volunteers.¹¹ The second more robust study by Malik and colleagues evaluated both idiopathic and diabetic gastroparesis and demonstrated an inverse correlation with diameter and cross-sectional area of the pylorus with early satiety and post-prandial fullness.¹² Additionally, the basal pyloric pressure was observed to be elevated in almost half of the patients with nausea and vomiting and delayed gastric emptying. Interestingly, in contrast to the authors’ hypothesis, no differences were found between idiopathic gastroparesis and diabetic gastroparesis.

It is therefore reasonable to conclude that pyloric dysfunction exists in at least a subset of patients with gastroparesis. However, the functional significance of this finding remains unknown. Intuitively, this may contribute to delayed gastric emptying; however, gastric emptying rates do not correlate well with symptoms of gastroparesis.¹³ Histological data from patients with idiopathic gastroparesis and diabetic gastroparesis- loss of interstitial cells of Cajal are seen in both subsets of patients as well as increased macrophage infiltration- suggest that the pathogenesis of the condition and associated symptoms may be more complex than previously thought.¹⁴ What we call gastroparesis may indeed represent a spectrum of gastric neuromuscular disorders, only some of which are associated with delayed emptying, despite the presence of similar symptoms.¹⁵ By extension, pyloric dysfunction may also be a merely a manifestation of the disease, a confounding factor, or one of its culprits. Nonetheless, based on the speculation that pyloric dysfunction is responsible for the delay in gastric emptying seen in gastroparesis, an argument has been made to target the sphincter using botulinum neurotoxin injections, pyloroplasty and pyloromyotomy,¹⁶ as well as pyloric stenting.¹⁷ We will examine the safety and efficacy of botulinum neurotoxin in gastroparesis more carefully below.

Therapeutic use of botulinum toxin

Botulinum neurotoxin (BoNT) was first suggested for therapeutic application in the early nineteenth century by German medical officer Christian Kerner who experimented with the (as yet unidentified) toxin in animal models to demonstrate its ability to cause paralysis of the skeletal muscles and loss of parasympathetic function.¹⁸ Produced by *Clostridium botulinum*, BoNT blocks the release of the neurotransmitter acetylcholine from the presynaptic terminal. This interferes with synaptic vesicle-plasma membrane fusion at the

neuromuscular junction in both skeletal motor endplates and in visceral organs, resulting in functional paralysis for a variable period of time typically in the range of several months.

There are three commercially available BoNT formulations in the United States: BOTOX (Allergan Inc., California), Neuroblock® or Myobloc® (US World Meds, Louisville, Kentucky), and Dysport (Ipsen Ltd, Slough, UK). Despite being one of the most deadly neurotoxins known, the therapeutic administration of BoNT is quite safe in the miniscule dosages used clinically. A meta-analysis examining the use of BOTOX in a variety of diseases found that focal weakness at the site of the injection was the sole consistent adverse event compared to controls.¹⁹

Today BoNT is widely used in a variety of neurological, ophthalmological, urological, dermatologic, gastrointestinal, orthopedic, and cosmetic conditions.^{20, 21} Only a handful of these are approved by the FDA and the rest are considered off-label use. Experimentation in spastic disorders of smooth muscle in the gastrointestinal tract was catalyzed after the toxin was first used successfully as a treatment for achalasia in 1995.²² Subsequent applications include esophageal spasm, sphincter of Oddi dysfunction, anal fissure, anismus, gastroparesis, and more recently obesity.^{23, 24}

For gastroparesis, BoNT is typically delivered endoscopically as an intrapyloric injection usually under direct visualization. A sclerotherapy needle (23 or 25 G) is advanced through the biopsy channel and typically 20-25 U BoNT/mL are injected into each of its four quadrants. Normally, patients can be discharged and diet advanced as tolerated on the same day as the procedure. An endoscopic ultrasonography-guided approach has also been described to increase precision of delivery to the pyloric sphincter.²⁵

Botulinum toxin in gastroparesis: clinical outcomes

Several studies in human adults have been published on this topic,²⁶⁻⁴³ two of which were randomized control trials conducted by Arts and colleagues in 2007 and Friedenberg and colleagues in 2008.^{36, 39} The results of the major studies are summarized in Table 1. Most studies involved small samples sizes and did not evaluate pyloric function before or after the intervention. We will discuss some highlights of these trials below.

In 2002, Ezzedine and colleagues published an open label trial of six patients with diabetic gastroparesis who underwent pyloric injection of 100 units of BoNT.²⁶ There was an average symptom improvement of 55% at 6 weeks post-procedure. Furthermore, the average solid phase gastric emptying study improved from 27.8% to 49% at 6 weeks. The data from this small trial showed promise as did three limited additional open label prospective trials published the same year, each demonstrating clinical improvement after treatment.²⁶⁻²⁸ Among these, Miller and colleagues demonstrated subjective improvement in 9 out of 10 female patients with idiopathic gastroparesis for more than 24 weeks after treatment with 80-100 units of BoNT.²⁸ 70% of patients in this study had improved gastric emptying study with solids, however, no patients had improvement to liquids. Of note, half of these patients required repeat BoNT injections due to symptom recurrence, although all noted improvement after the second injection as well. These data were promising while also highlighting the likelihood of the need for repeated injections if BoNT is used long-term.

This raises concern for the consequences of possible scarring to the pylorus, potentially worsening the pyloric dysfunction that the treatment aims to mitigate. In BoNT for achalasia, repeated injections have been shown to lead to submucosal fibrosis, rendering future surgical myotomy more difficult.⁴⁴

Following these studies, Bromer and colleagues published a single-center retrospective study in 2005 evaluating 63 patients with gastroparesis (35 idiopathic, 26 diabetic, and 2 post-operative), which at that time was the largest study to date.³² Pyloric BoNT injection of 100-200 units resulted in improved symptoms in 43% of cases, however, this benefit only lasted approximately 2 months. Additionally, male gender was associated with a response to treatment, and a predominant symptom of vomiting predicted a poor response to treatment. Of note, a higher dose of BoNT injection was not associated with a positive response in this limited study. An important limitation of this study was that the subjects did not undergo gastric emptying studies or manometry following treatment, unlike the previous smaller studies that included some form of objective measurement.

Based on the promise of these early studies, researchers designed two controlled studies published soon thereafter. In the first of these, 23 patients with gastroparesis (19 with idiopathic disease) underwent two upper endoscopies at 4 week intervals with either injection of saline or 100 U BoNT in a randomized, double-blind cross-over design.³⁶ Perhaps somewhat surprisingly, significant improvement in symptoms using the validated Gastroparesis Cardinal Symptom Index (GCSI)⁴⁵ and gastric emptying was seen after initial injection of both saline or BoNT. The authors therefore concluded that BoNT was not superior to placebo, and suggested the occurrence of “a major placebo effect after endoscopic injection therapy.” A second randomized control trial was designed by Friedenberg and colleagues examining 32 patients with diabetic or idiopathic gastroparesis.³⁹ Saline or 200 units of BoNT were injected in a randomized blinded fashion and patients were followed up after 4 weeks. As with the study performed by Arts and colleagues, this trial failed to demonstrate a difference in outcomes between placebo and injection. Interestingly, again, both placebo and injection resulted in improvements in GCSI; however, only BoNT appeared to cause significant improvement in gastric emptying. This may be important because it implies that the BoNT injections may have had the desired physiological effect, but yet clinically was no different than placebo, emphasizing the discrepancy between gastric emptying and symptoms. Additionally, the larger dose of BoNT overcame the limitation posed by the Arts study where some doubt remained whether a benefit could be elicited by a relatively smaller dose of 100 U. This study was limited by low statistical power (it was based on an assumption of 80% response rate), but nonetheless, coupled with the other randomized control trial, its results discouraged further routine use of BoNT in gastroparesis. Of note, both randomized control trials enrolled a heterogeneous gastroparesis population, which may also potentially represent a confounding factor.

In 2009, Coleski and colleagues published the largest study to date on this subject- a retrospective open-label cohort of 179 patients (81 diabetic and 79 idiopathic)- with a goal of elucidating factors that may enhance response to therapy.⁴¹ They demonstrated that a greater clinical response corresponded to higher doses of BoNT injection (200 units versus 100 units). Their analysis also suggested that patients with idiopathic gastroparesis, women,

and age less than 50 years old were more likely to respond to BoNT injections (this contrasted with the Bromer study demonstrating a more likely clinical response in men). Given that BoNT therapy has been shown to be no better than placebo in control studies, the interpretation of these open-label results is hazardous at best. However, this study added important data points to the conversation regarding how to potentially target subjects for a more selective future clinical trial.

In the past year, a study was published by researchers at Wake Forest on the effect of BoNT (given in 100 U doses) or pyloric balloon dilation on patients with gastroparesis who had documented normal electrogastrograms (3 cycles per minute).⁴² The authors hypothesized that the pathophysiological mechanism of gastroparesis in these patients was pyloric dysfunction (and not a problem with stomach corpus) and therefore were an appropriately targeted patient population for this intervention. In their retrospective cohort analysis involving thirty-three patients (25 of whom underwent BoNT injections and 8 underwent balloon dilation), 78% percent reported an improvement of symptoms for at least 4 weeks. Notably, the authors did not stratify their results based on the type of pyloric therapy received, and so conclusions cannot be drawn further on the specific effect of BoNT in gastroparesis. As with other studies, these results must be viewed with caution in light of the previous randomized control trials.

Taken together, the studies published on BoNT in gastroparesis to date have significant limitations. As discussed, it has been argued that one reason for the failure of these studies to demonstrate a positive treatment effect is the incorrect selection of patients most likely to benefit, that is, lacking pyloric dysfunction at baseline. Neither of the two randomized control trials measured pyloric function after BoNT injection, therefore it is unclear if BoNT truly had the anticipated physiologic effect, aside from the hypothesized clinical effect. However, at least in the trial performed by Friedenbergs and colleagues, BoNT improved gastric emptying compared to placebo.³⁹ Technical issues may also have contributed to these results. There remains no data regarding the ideal depth and location of the injection (many endoscopists favor a four-quadrant approach), and inadvertent diffusion of BoNT into the gastric antrum is possible. While more technically challenging, injections directed into the pyloric channel or proximal duodenal bulb using endoscopic ultrasound (EUS) guidance may be a superior approach for this type of treatment. Perhaps most importantly, the reason this intervention may be unsuccessful is that there is no evidence of a causal relationship between pyloric dysfunction delayed emptying and the symptoms of gastroparesis. It is therefore possible that even in patients with documented pyloric dysfunction who receive adequate BoNT injections, dysmotility in other critical regions of the GI tract precluded a robust symptomatic response to this treatment.

Conclusion and future directions

Gastroparesis is a heterogeneous motility disorder for which a definitive cause is not identified in the majority of patients. While early studies regarding the use of BoNT in gastroparesis carried hope for a relatively safe and efficacious treatment modality, more rigid analyses and randomized control trials are unable to support its use. A systematic review of the literature published by Bai and colleagues in 2010 concluded that there was no evidence

to recommend botulinum toxin injection for gastroparesis.⁴⁶ This sentiment is echoed in the ACG clinical guidelines on the management of gastroparesis published in 2012.⁴⁷ Nonetheless, BoNT is still administered at many institutions for refractory patients, underscoring both the paucity of available treatments for patients living with this disabling condition and the critical need for further larger-scale studies. A more recent review of the literature published by Ukleja and colleagues in 2015 argued that given the limited treatment options, “botox injections can still be considered as treatment option” for patients when other therapies have failed.⁴⁸ Additionally, in patients such as lung transplant patients where the possible sequelae of gastroparesis (i.e. gastric reflux leading to aspiration) may lead to graft failure, it has been proposed that the benefits of this relatively benign procedure may outweigh the risks.⁴³

At this time there is no scientific evidence to support the use of BoNT in clinical practice for patients with gastroparesis. We do think the field may benefit from further research and carefully conducted prospective clinical trials. Researchers should consider three important questions before nailing the coffin shut on BoNT in gastroparesis. First, is there a subset of patients with gastroparesis for whom this treatment would be truly beneficial and how to identify and target such a population? As a corollary, are endoFLIP or manometry sufficient to identify patients who may benefit or do other patient characteristics influence their likely response such as age, gender, or suspected cause of gastroparesis? Additionally, if the clinical response to BoNT is dose-dependent as has been reported, then what dosage should be considered therapeutic? Lastly, as accurate administration of BoNT is ultimately dependent on the skills of the endoscopist, the possibility exists that the injections do not precisely reach the pylorus. Therefore, should EUS guided injections be used and adequate delivery of the drug be routinely quantified (e.g. with pre- and post-procedure pyloric measurements) to determine at very least if the BoNT achieved its pharmacological intention before assessing clinical response? Unless further rigorous studies demonstrate its clinical efficacy, BoNT for gastroparesis may begin to fade into the background as alternative modalities emerge for refractory patients. A newer technique, gastric peroral endoscopic myotomy, or G-POEM, is an interesting approach to treatment of gastroparesis, first described by Khashab and colleagues in 2013.⁴⁹ However, this approach should also be considered highly experimental as it is based on the same fundamental presumptions that prompted the use of BoNT. It is not clear that simply having more robust ablation of the sphincter will be helpful to improve symptoms of gastroparesis if the basis of these symptoms lies elsewhere. The literature is replete with unfulfilled promises suggested by open-label studies for functional and motility bowel disorders. As we have discussed in this review, randomized clinical trials often fail to validate these initial findings despite the enthusiasm of the early adopters. In this regard, we have learnt many valuable lessons from BoNT, and for the sake of our patients, we should not continue to offer therapies that have not withstood the test of rigorously designed and conducted clinical trials.

It is evident that there are no easy fixes for gastroparesis and that it will remain a challenging disorder to treat. True progress will only come when we can confidently identify the pathophysiological basis of symptoms and the cellular and molecular pathogenesis of this condition. We can then begin to develop disease-modifying agents that go beyond our palliative approaches and provide real value to long-suffering patients.

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References

- Hasler WL, Parkman HP, Wilson LA, et al. Psychological Dysfunction Is Associated With Symptom Severity but Not Disease Etiology or Degree of Gastric Retention in Patients With Gastroparesis. *The American Journal of Gastroenterology* 2010;105:2357–2367. [PubMed: 20588262]
- Parkman HP, Yates K, Hasler WL, et al. Similarities and Differences Between Diabetic and Idiopathic Gastroparesis. *Clinical Gastroenterology and Hepatology* 2011;9:1056–1064. [PubMed: 21871247]
- Mearin F, Camilleri M, Malagelada J-R. Pyloric dysfunction in diabetics with recurrent nausea and vomiting. *Gastroenterology* 1986;90:1919–1925. [PubMed: 3699409]
- Feldman M, Smith HJ, Simon TR. Gastric emptying of solid radiopaque markers: studies in healthy subjects and diabetic patients. *Gastroenterology* 1984;87:895–902. [PubMed: 6468877]
- Horowitz M, Harding PE, Chatterton BE, et al. Acute and chronic effects of domperidone on gastric emptying in diabetic autonomic neuropathy. *Digestive Diseases and Sciences* 1985;30:1–9. [PubMed: 3965269]
- Loo FD, Palmer DW, Soergel KH, et al. Gastric emptying in patients with diabetes mellitus. *Gastroenterology* 1984;86:485–94. [PubMed: 6693013]
- Schade RR, Dugas MC, Lhotsky DM, et al. Effect of metoclopramide on gastric liquid emptying in patients with diabetic gastroparesis. *Digestive Diseases and Sciences* 1985;30:10–15. [PubMed: 3965270]
- Snape WJ. Metoclopramide to Treat Gastroparesis due to Diabetes Mellitus. *Annals of Internal Medicine* 1982;96:444. [PubMed: 7065559]
- Ata-Lawenko RM, Lee YY. Emerging Roles of the Endolumenal Functional Lumen Imaging Probe in Gastrointestinal Motility Disorders. *Journal of Neurogastroenterology and Motility* 2017;23:164–170. [PubMed: 28013295]
- McMahon BP, Frøkjær JB, Kunwald P, et al. The functional lumen imaging probe (FLIP) for evaluation of the esophagogastric junction. *American Journal of Physiology- Gastrointestinal and Liver Physiology* 2007;292:G377–G384. [PubMed: 16950760]
- Gourcerol G, Tissier F, Melchior C, et al. Impaired fasting pyloric compliance in gastroparesis and the therapeutic response to pyloric dilatation. *Alimentary Pharmacology & Therapeutics* 2014;41:360–367. [PubMed: 25523288]
- Malik Z, Sankineni A, Parkman HP. Assessing pyloric sphincter pathophysiology using EndoFLIP in patients with gastroparesis. *Neurogastroenterology & Motility* 2015;27:524–531. [PubMed: 25712043]
- Pasricha PJ, Colvin R, Yates K, et al. Characteristics of Patients With Chronic Unexplained Nausea and Vomiting and Normal Gastric Emptying. *Clinical Gastroenterology and Hepatology* 2011;9:567–576.e4. [PubMed: 21397732]
- Grover M, Farrugia G, Lurken MS, et al. Cellular Changes in Diabetic and Idiopathic Gastroparesis. *Gastroenterology* 2011;140:1575–1585.e8. [PubMed: 21300066]
- Harer KN, Pasricha PJ. Chronic Unexplained Nausea and Vomiting or Gastric Neuromuscular Dysfunction (GND)? An Update on Nomenclature, Pathophysiology and Treatment, and Relationship to Gastroparesis. *Curr Treat Options Gastroenterol* 2016;14:410–419. [PubMed: 27722801]
- Hibbard ML, Dunst CM, Swanström LL. Laparoscopic and Endoscopic Pyloroplasty for Gastroparesis Results in Sustained Symptom Improvement. *Journal of Gastrointestinal Surgery* 2011;15:1513–1519. [PubMed: 21720926]
- Clarke J, Sharaiha R, Kord Valeshabad A, et al. Through-the-scope transpyloric stent placement improves symptoms and gastric emptying in patients with gastroparesis. *Endoscopy* 2013;45:E189–E190. [PubMed: 23824975]
- Monheit GD, Pickett A. AbobotulinumtoxinA: A 25-Year History. *Aesthet Surg J* 2017;37:S4–S11.

19. Naumann M, Jankovic J. Safety of botulinum toxin type A: a systematic review and meta-analysis. *Current Medical Research and Opinion* 2004;20:981–990. [PubMed: 15265242]
20. Dutta SR, Passi D, Singh M, et al. Botulinum toxin the poison that heals: A brief review. *Natl J Maxillofac Surg* 2016;7:10–16. [PubMed: 28163472]
21. Jankovic J Botulinum toxin: State of the art. *Movement Disorders* 2017;32:1131–1138. [PubMed: 28639368]
22. Pasricha PJ, Ravich WJ, Hendrix TR, et al. Intraspincteric botulinum toxin for the treatment of achalasia. *N Engl J Med* 1995;332:774–8. [PubMed: 7862180]
23. Bang CS, Baik GH, Shin IS, et al. Effect of intragastric injection of botulinum toxin A for the treatment of obesity: a meta-analysis and meta-regression. *Gastrointestinal Endoscopy* 2015;81:1141–1149.e7. [PubMed: 25765772]
24. Friedenberg F, Gollamudi S, Parkman HP. REVIEW: The Use of Botulinum Toxin for the Treatment of Gastrointestinal Motility Disorders. *Digestive Diseases and Sciences* 2004;49:165–175. [PubMed: 15104353]
25. Yin G, Tan W, Hu D. Endoscopic ultrasonography-guided intrapyloric injection of botulinum toxin to treat diabetic gastroparesis. *Digestive Endoscopy* 2016;28:759–759. [PubMed: 27556873]
26. Ezzeddine D, Jit R, Katz N, et al. Pyloric injection of botulinum toxin for treatment of diabetic gastroparesis. *Gastrointestinal Endoscopy* 2002;55:920–923. [PubMed: 12024156]
27. Lacy B Botulinum toxin for the treatment of gastroparesis: a preliminary report. *The American Journal of Gastroenterology* 2002;97:1548–1552. [PubMed: 12094882]
28. Miller L Treatment of idiopathic gastroparesis with injection of botulinum toxin into the pyloric sphincter muscle. *The American Journal of Gastroenterology* 2002;97:1653–1660. [PubMed: 12135014]
29. Gupta P, Rao SSC. Attenuation of isolated pyloric pressure waves in gastroparesis in response to botulinum toxin injection: A case report. *Gastrointestinal Endoscopy* 2002;56:770–772. [PubMed: 12397299]
30. Woodward MN, Spicer RD. Intrapyloric Botulinum Toxin Injection Improves Gastric Emptying. *Journal of Pediatric Gastroenterology and Nutrition* 2003;37:201–202. [PubMed: 12883311]
31. Lacy BE, Crowell MD, Schettler-Duncan A, et al. The Treatment of Diabetic Gastroparesis With Botulinum Toxin Injection of the Pylorus. *Diabetes Care* 2004;27:2341–2347. [PubMed: 15451898]
32. Bromer MQ, Friedenberg F, Miller LS, et al. Endoscopic pyloric injection of botulinum toxin A for the treatment of refractory gastroparesis. *Gastrointestinal Endoscopy* 2005;61:833–839. [PubMed: 15933684]
33. Ben-Youssef R, Baron PW, Franco E, et al. Intrapyloric Injection of Botulinum Toxin A for the Treatment of Persistent Gastroparesis Following Successful Pancreas Transplantation. *American Journal of Transplantation* 2006;6:214–218. [PubMed: 16433778]
34. Tcherniak A, Kashtan DH, Melzer E. Successful Treatment of Gastroparesis Following Total Esophagectomy Using Botulinum Toxin. *Endoscopy* 2006;38:196–196. [PubMed: 16479431]
35. Dumonceau J, Giostra E, Bech C, et al. Acute Delayed Gastric Emptying after Ablation of Atrial Fibrillation: Treatment with Botulinum Toxin Injection. *Endoscopy* 2006;38:543–543. [PubMed: 16767599]
36. Arts J, Holvoet L, Caenepeel P, et al. Clinical trial: a randomized-controlled crossover study of intrapyloric injection of botulinum toxin in gastroparesis. *Alimentary Pharmacology & Therapeutics* 2007;26:1251–1258. [PubMed: 17944739]
37. Arts J, Van Gool S, Caenepeel P, et al. Influence of intrapyloric botulinum toxin injection on gastric emptying and meal-related symptoms in gastroparesis patients. *Alimentary Pharmacology & Therapeutics* 2006;24:661–667. [PubMed: 16907899]
38. Kent MS, Pennathur A, Fabian T, et al. A pilot study of botulinum toxin injection for the treatment of delayed gastric emptying following esophagectomy. *Surgical Endoscopy* 2007;21:754–757. [PubMed: 17458616]
39. Friedenberg FK, Palit A, Parkman HP, et al. Botulinum Toxin A for the Treatment of Delayed Gastric Emptying. *The American Journal of Gastroenterology* 2008;103:416–423. [PubMed: 18070232]

40. Mirbagheri SA, Sadeghi A, Amouie M, et al. Pyloric Injection of Botulinum Toxin for the Treatment of Refractory GERD Accompanied with Gastroparesis: A Preliminary Report. *Digestive Diseases and Sciences* 2008;53:2621–2626. [PubMed: 18256933]
41. Coleski R, Anderson MA, Hasler WL. Factors Associated with Symptom Response to Pyloric Injection of Botulinum Toxin in a Large Series of Gastroparesis Patients. *Digestive Diseases and Sciences* 2009;54:2634–2642. [PubMed: 19184429]
42. Wellington J, Scott B, Kundu S, et al. Effect of endoscopic pyloric therapies for patients with nausea and vomiting and functional obstructive gastroparesis. *Autonomic Neuroscience* 2017;202:56–61. [PubMed: 27460691]
43. Hoofn N, Smith M, Huang J, et al. Gastroparesis is common after lung transplantation and may be ameliorated by botulinum toxin-A injection of the pylorus. *The Journal of Heart and Lung Transplantation* 2014;33:1314–1316. [PubMed: 25443873]
44. Patti MG, Feo CV, Arcerito M, et al. The effects of previous treatment on the results of myotomy for achalasia. *Gastroenterology* 1998;114:A254.
45. Revicki DA, Rentz AM, Dubois D, et al. Development and validation of a patient-assessed gastroparesis symptom severity measure: the Gastroparesis Cardinal Symptom Index. *Alimentary Pharmacology and Therapeutics* 2003;18:141–150. [PubMed: 12848636]
46. Bai Y, Xu M-J, Yang X, et al. A Systematic Review on Intr pyloric Botulinum Toxin Injection for Gastroparesis. *Digestion* 2010;81:27–34. [PubMed: 20029206]
47. Camilleri M, Parkman HP, Shafi MA, et al. Clinical Guideline: Management of Gastroparesis. *The American Journal of Gastroenterology* 2012;108:18–37. [PubMed: 23147521]
48. Ukleja A, Tandon K, Shah K, et al. Endoscopic botox injections in therapy of refractory gastroparesis. *World Journal of Gastrointestinal Endoscopy* 2015;7:790. [PubMed: 26191343]
49. Khashab MA, Stein E, Clarke JO, et al. Gastric peroral endoscopic myotomy for refractory gastroparesis: first human endoscopic pyloromyotomy (with video). *Gastrointestinal Endoscopy* 2013;78:764–768. [PubMed: 24120337]

KEY POINTS

- Botulinum toxin injections for gastroparesis is based on the hypothesis that amelioration of pyloric dysfunction among a subset of patients will lead to symptomatic improvement
- While several open-label studies showed initial promise, no data exists demonstrating causality between pyloric dysfunction and symptoms of gastroparesis
- Two randomized clinical trials have failed to demonstrate a difference in clinical outcomes between botulinum toxin versus placebo in gastroparesis
- Based on current evidence, further use of botulinum toxin for gastroparesis is discouraged outside of a research setting

SYNOPSIS

Refractory gastroparesis is among the most difficult therapeutic challenges in gastroenterology. Pyloric dysfunction has been described in a subset of patients with gastroparesis, prompting experimentation with botulinum toxin injections into the pylorus, which is relatively safe and has been successfully used in other gastrointestinal disorders. However, causality between pyloric dysfunction and symptoms of gastroparesis has never been demonstrated. While several open-label studies showed initial promise, two randomized clinical trials failed to elicit a difference in clinical outcomes in botulinum toxin versus placebo. Based on current evidence, further use of botulinum toxin for gastroparesis is discouraged outside of a research trial.

Table 1.

Summary table of important trials in the study of BoNT for gastroparesis.

Source study	Number of patients	Study design	Etiology of gastroparesis	BoNT Dose (IU)	Assessment of pyloric function?	Subjective outcomes	Objective outcomes
Ezzeddine et al (2002) ²⁶	6	Prospective, open-label	DM	100	No	Significant improvement in symptoms at 6 weeks	Significant improvement in gastric emptying at 6 weeks
Miller et al (2002) ²⁸	10	Prospective, open-label	idiopathic	80-100	No	90% patients with significant improvement in symptoms at 4 weeks	70% patients demonstrated improvement in solid emptying at 4 weeks, no improvement in liquids
Bromer et al (2005) ³²	63	Retrospective, open-label	Idiopathic (35), DM (26), post-operative (2)	100 or 200	No	~43% patients with improved symptoms lasting ~5 months	Not evaluated
Arts et al (2007) ³⁶	23	Randomized controlled, double-blind, crossover	Idiopathic (19), DM (2), post-operative (2)	100	No	No difference	No difference
Friedenberg et al (2008) ³⁹	32	Randomized controlled, double-blind	DM (18), idiopathic (13), post-operative (1)	200	No	No difference	Improved gastric emptying at 4 weeks
Coleski et al (2009) ⁴¹	179	Retrospective, open-label	DM (81), Idiopathic (79)	100, 150 or 200	No	~51% patients with improved symptoms at 1-4 weeks	Not evaluated
Hoofst et al (2014) ⁴³	13	Retrospective, open-label	Post-operative	100	No	Not evaluated	Improved gastric emptying in 76% patients at 4 weeks