

Botulinum Toxin and Gastrointestinal Tract Disorders: Panacea, Placebo, or Pathway to the Future?

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Abstract: The history of botulinum toxin is fascinating. First recognized as the cause of botulism nearly 200 years ago, it was originally feared as a deadly poison. Over the last 30 years, however, botulinum toxin has been transformed into a readily available medication used to treat a variety of medical disorders. Interest in the use of botulinum toxin has been particularly strong for patients with spastic smooth muscle disorders of the gastrointestinal tract. Patients with achalasia, diffuse esophageal spasm, gastroparesis, sphincter of Oddi dysfunction, and anal fissures have all been treated with botulinum toxin injections, often with impressive results. However, not all patients respond to botulinum toxin therapy, and large randomized controlled trials are lacking for many conditions commonly treated with botulinum toxin. This paper reviews the history, microbiology, and pharmacology of botulinum toxin, discusses its mechanism of action, and then presents recent evidence from the literature regarding the use of botulinum toxin for the treatment of a variety of gastrointestinal tract disorders.

The first article to describe the clinical use of botulinum toxin (BTX), in nonhuman primates, was published in 1973.¹ Nearly twenty years later, Pasricha and colleagues reported on the use of BTX in the gastrointestinal (GI) tract.² This novel study demonstrated that BTX could be safely injected into the smooth muscle of the GI tract and that it decreased resting pressure of the lower esophageal sphincter (LES) in piglets. This simple trial, which was not widely recognized or appreciated at the time, opened up an entirely new field of research and therapy for many GI motility disorders. Over the last 15 years, the use of BTX in the GI tract has spread well beyond that in the lower esophagus. For some disorders, treatment with BTX dramatically improves or resolves symptoms. Yet for other disorders, BTX appears to be no better than placebo. This paper will review the microbiology, pharmacology, and mechanism of action of BTX, and it will provide an overview of the current and future uses of BTX in the GI tract. This article is not meant to be an exhaustive review of the literature but will instead focus on recent data published in

Keywords

Achalasia, anal fissure, botulinum toxin, esophagus, gastroparesis, obesity, sphincter of Oddi

peer-reviewed journals, where available. Articles were identified by performing MEDLINE (1966–2007) and PubMed (1970–2007) searches using the following keywords both individually and in combination with botulinum toxin and botox: structure, mechanism of action, pharmacology, esophagus, achalasia, lower esophageal sphincter, nutcracker esophagus, diffuse esophageal spasm, hypertensive lower esophageal sphincter, stomach, gastric, pylorus, gastroparesis, sphincter of Oddi, gastroduodenal, diabetes, constipation, anal fissure, anismus, rectocele, hemorrhoids, proctalgia fugax, puborectalis syndrome, outlet obstruction, and pelvic floor dysfunction. References were reviewed in each article for additional relevant articles.

Microbiology

Clostridia are gram-positive, spore-forming, obligate, anaerobic bacilli widely present in soil, water, and the GI tract of most animals and nearly all humans. Approximately 50 different species are present in normal human fecal flora. One of these species, *Clostridium (C.) botulinum*, produces a neurotoxin responsible for causing botulism, a symmetric, descending, paralytic illness of motor and autonomic nerves that causes death in up to 10–25% of cases.³ Toxin exposure generally occurs via colonization of the lower GI tract after the ingestion of a contaminated meal. Typical symptoms include blurring of vision, ptosis, diplopia, dysphonia, dysarthria, dysphagia, and generalized muscle weakness, which can lead to respiratory failure and death.³

There are 8 different serotypes of *C. botulinum* (A, B, C1, C2, D, E, F, and G), though human botulism is primarily caused by serotypes A, B, and E. Although structurally similar, these serotypes are antigenically distinct. BTX is considered the most potent lethal substance known to humankind. It is estimated that the lethal dose in humans is approximately 3,000–5,000 U (approximately 1×10^{-8} g) of BTX A. Most cases of botulism occur after eating contaminated canned foods that have not been heated long enough, prior to canning, to kill the spores or destroy the toxin. The toxin can be destroyed by boiling for 5–10 minutes or heating to 85° C for 30 minutes. Spores are more heat-resistant and require temperatures as high as 120° C in order to be destroyed.

Historical Background

Botulism likely dates as far back as humankind has tried to preserve food, though our earliest accurate historical records are from the 18th and 19th centuries, when botulism was initially described as “sausage poisoning.” (*Botulus* is the Latin term for sausage). Justinius Kerner

(1786–1862), a German physician, poet, and philosopher, first recognized the connection between blood sausage poisoning and paralytic illness. In 1820, while working as a district health officer in southern Germany, he published a summary of 76 cases of botulism.^{4,5} Kerner is also credited as the first person to consider the potential use of BTX in disorders of muscle spasticity and hypertonicity.

The pathogenesis of botulism was first described by van Ermengem in 1897 when he demonstrated that *Clostridium* produced a substance that caused muscle weakness in animals.⁶ Type A neurotoxin was isolated in 1920, though large-volume concentration and crystallization were not achieved until 1946.⁷ BTX A was used clinically for the first time in 1977 in strabismus patients.⁸ The US Food and Drug Administration (FDA) approved BTX A (Botox, Allergan) for the treatment of strabismus, cervical dystonia, and blepharospasm in 1989 in patients 12 years of age and older, though it is also commonly used to treat torticollis, ophthalmoplegia, and other spastic disorders of skeletal muscle. In 2002, the FDA approved the use of BTX A for cosmetic purposes (brow-furrow wrinkles) and then for axillary hyperhidrosis in 2004. BTX type B (Myobloc, Solstice Neurosciences) was approved by the FDA for the treatment of blepharospasm and cervical dystonia in 2000. Of note, although commonly used to treat a variety of GI disorders, the FDA has not approved the use of BTX A or B for any specific use in the GI tract.

Structure, Pharmacology, and Mechanism of Action

BTX is initially synthesized as an inactive, single-chain polypeptide that is then cleaved into a high molecular weight (150 kilodalton), dichain structure linked by a single disulfide bond (Figure 1). The heavy chain (100 kilodalton), identical for all 8 toxin types, binds specifically to the presynaptic membrane of cholinergic nerve terminals, while the light chain (50 kilodalton) is internalized and blocks neurotransmitter release (as discussed below). The light chain is a zinc-dependent endoprotease (metalloprotease) and is structurally distinct for all 8 toxin subtypes.

BTX A blocks neuromuscular conduction by inhibiting the release of acetylcholine (ACh) at the neuromuscular junction (NMJ). The release of ACh at the NMJ occurs through assembly of a synaptic fusion complex and a set of soluble N-ethylmaleimide-sensitive fusion attachment protein receptor (SNARE) proteins that include a synaptosomal-associated protein of 25 kd (SNAP-25). BTX A inhibits the exocytotic release of ACh through four key steps: binding to the plasma membrane of presynaptic

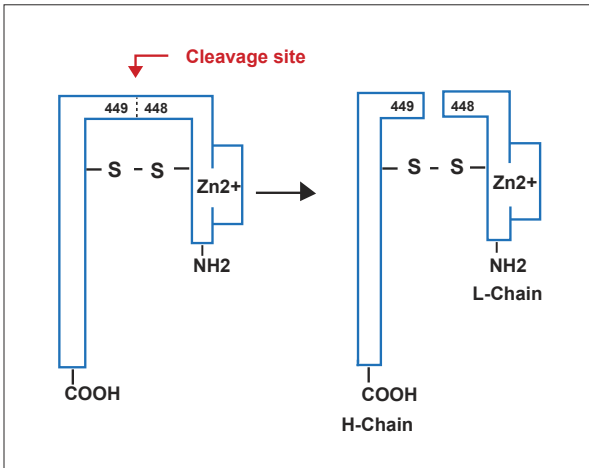


Figure 1. Structure of botulinum toxin A.

neurons; uptake into nerve terminals through endocytosis; cleavage of key proteins involved in exocytosis; and interruption of the docking and release of ACh vesicles from nerve terminals (Figure 2). Specifically, the heavy chain binds to a receptor on nerve terminals and enters the cell through endocytosis. Once in the cell, the light chain, a Zn²⁺-dependent protease, becomes activated and hydrolyzes the SNARE complex involved in exocytosis, which includes SNAP-25. SNAP-25 is integral to the docking and release of ACh from vesicles at nerve endings. The

prevention of calcium-dependent release of ACh results in a state of partial chemical denervation of the striated muscle, decreased local muscle contractility, and local paralysis. Paralysis is transient, as slow reversal of muscle denervation occurs secondary to axonal sprouting and development of extrajunctional ACh.⁹⁻¹² BTX A acts on all cholinergic nerve terminals, including those of motor neurons, preganglionic sympathetic and parasympathetic neurons, and postganglionic parasympathetic nerves.

In addition to the effects of BTX on cholinergic nerves, there is also evidence to suggest that BTX may act on noncholinergic fibers as well. BTX A appears to have an antinociceptive action independent of its paralytic effect, potentially preventing the release of glutamate, which subsequently mediates the release of substance P.¹³ Furthermore, an analgesic effect may occur through alteration of autonomic function and regional blood flow.¹³

Pathology

One of the major limitations of BTX is its transience. The toxin binds to the presynaptic membrane and blocks ACh release; however, this effect diminishes as the presynaptic membrane regenerates.¹⁴ This process of membrane regeneration is expedited by a reduction in ACh esterase activity, upregulation of extrajunctional ACh receptors, and increased lysosomal and endocytic activity.¹⁵⁻¹⁷ It is reasonable to assume that inhibition of these recovery mechanisms could significantly increase the duration and efficacy of BTX injections. In fact, several investigators

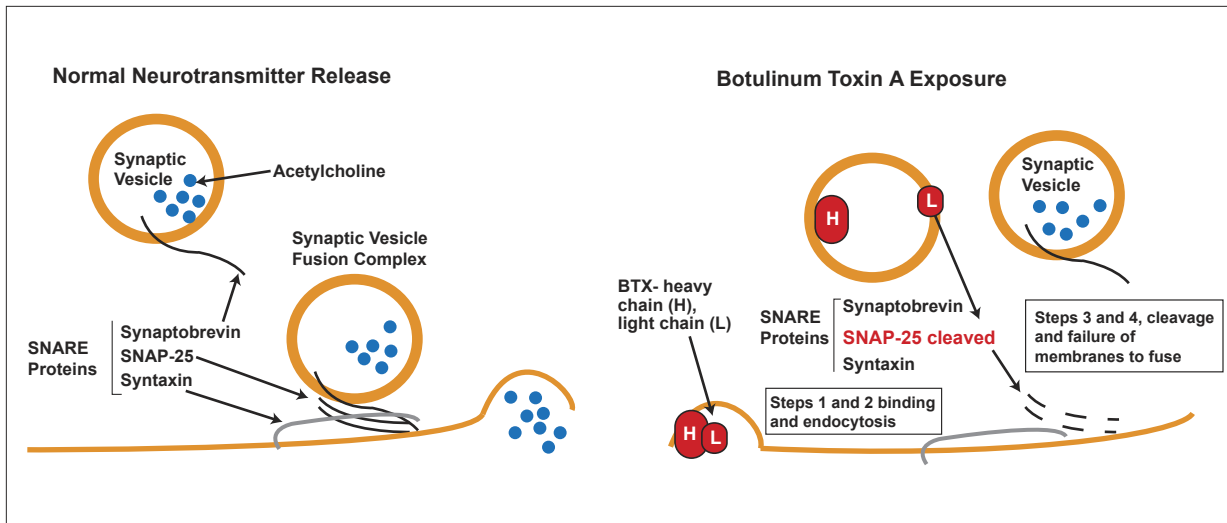


Figure 2. Mechanism of action of botulinum toxin A.

Modified from Arnon SS, et al.⁹

BTX=botulinum toxin; SNARE=soluble N-ethylmaleimide-sensitive fusion attachment protein receptor.

have speculated that diminished nerve regeneration due to aging might explain the better long-term response to BTX injections seen in elderly patients with achalasia.¹⁸

Other factors may also be critical for determining the efficacy of BTX injections. For example, data from a recent animal study suggest that BTX injections may cause shifts in the major histocompatibility complex of muscles.¹⁹ Other investigators endorse the central role of the insulin-like growth factor-1 signaling pathway after BTX injection²⁰ and hypothesize that BTX may have inhibitory effects on other neurotransmitters in addition to ACh.²¹

In addition, histologic studies have demonstrated that the natural history of BTX-induced ACh blockade reflects the growth of a sprouting network that effectively bypasses the paralyzed NMJ.^{22,23} As the parent terminal recovers its ability to release ACh, the sprouting network slowly loses its activity and is eliminated. Recognition of these molecular findings may allow future investigators to modify and perhaps optimize the toxin's effects.

Uses in the Gastrointestinal Tract

Esophagus

Achalasia The neuromuscular disorder achalasia is characterized by impaired relaxation of the LES with concomitant esophageal aperistalsis. Surgical myotomy is considered the definitive treatment, though endoscopic therapies, including pneumatic dilation and more recently BTX injection, can also treat symptoms of achalasia. The earliest clinical studies were conducted by Pasricha and colleagues in the 1990s, after preliminary studies in piglets.² The initial studies compared BTX to placebo injections of saline and employed a protocol (80 U total of BTX A injected in all 4 quadrants above the z-line) that has not changed dramatically with time, though different doses and procedures have been investigated. These early studies suggested that BTX injection was safe, simple, and capable of short-term symptom reduction.²⁴ Since then, the definition of "short-term" has been revised repeatedly without clear consensus, as the efficacy of a single BTX injection has been found to vary from 3 months to 3 years.

The initial BTX-versus-placebo studies were followed by other studies comparing BTX to pneumatic dilation and myotomy. A recent Cochrane Collaboration meta-analysis reviewed the results of studies comparing endoscopic Rigiflex balloon dilation to BTX injection in patients with primary achalasia. Six studies involving 178 participants were compared; no significant difference in short-term remission (within 4 weeks of the initial intervention) was found, though the 6-month and 12-month remission rates were significantly greater after dilation.

The authors concluded that dilation was more effective than endoscopic treatment with BTX in the long term, defined as greater than 6 months.²⁵

To date, there has been only 1 randomized clinical trial comparing BTX injection to laparoscopic myotomy. This study demonstrated similar efficacy at 6-month follow-up, but a dramatic difference in long-term outcomes, with achalasia remission rates of 53% in the BTX group at 1 year posttreatment (vs 90% in the myotomy group) and 34% at 2 years (vs 88% postmyotomy).²⁰ It should be noted that other observational studies that were focused on the long-term efficacy of BTX have reported higher remission rates of 70–78% at 1 year and up to 54% at 2 years posttreatment.^{26,27}

At present, there are no published randomized, controlled trials comparing BTX, dilation, and myotomy. This is likely due to the divergent indications for each therapy. The most recent guidelines published by the American Gastroenterological Association regarding BTX injection in primary achalasia endorse this treatment for patients refractory to medical therapy or dilation, and for those patients deemed to be poor surgical candidates (eg, the elderly) who would not, in the clinician's assessment, tolerate medical therapy, dilation, or a complication of dilation.²⁸

Published studies have been analyzed in an attempt to identify factors that predict response to BTX injection, and these have demonstrated varying results. However, old age and the presence of vigorous achalasia are two factors that have correlated positively with response to BTX in multiple studies.^{18,29} As mentioned previously, the increased efficacy of BTX in the elderly may be due to reductions in presynaptic regeneration, thereby prolonging the toxin's effects.

With the advent of laparoscopic myotomy and minimally invasive surgery, pneumatic dilation is performed less frequently than in the past. With regard to BTX and surgical myotomy, there are substantial data regarding the effect of BTX pretreatment on surgical myotomy patients. Swine studies have shown that endoscopic pretreatment causes inflammation and fibrosis of the LES,³⁰ sparking concern that BTX injection might hinder subsequent LES myotomy. However, most studies have demonstrated that BTX injection does not affect muscle histology or patient outcome in patients undergoing subsequent surgical myotomy.^{31,32}

Nonachalasia Esophageal Disorders BTX has been evaluated in a number of other spastic esophageal motility disorders, including diffuse esophageal spasm (DES), isolated hypertensive LES, and "nutcracker esophagus." Hypocontractile disorders, including ineffective esophageal motility and hypotensive LES, are not amenable

to treatment with BTX. Cricopharyngeal dysphagia, a spastic disorder that responds well to BTX, is treated primarily by otolaryngologists, and two recent reviews have evaluated the use of BTX in this disorder.^{33,34}

Pathophysiologically, spastic esophageal motility disorders may develop due to defective nitrergic pathways and/or an imbalance in ACh and nitric oxide (NO) tissue levels. As there is some overlap between these spastic syndromes and achalasia, it is not surprising that BTX injections have improved symptoms in these disorders as well. A case report described the benefits of BTX A injection in the treatment of hypertensive LES,³⁵ and a case series demonstrated that BTX A injection reduced chest pain in 21 patients with nonreflux, nonachalasia, spastic esophageal motor disorders for a mean duration of 7.3 months (range=1–18 months).³⁶ Another small (N=9) case series showed comparable efficacy in this patient population, and the authors surmised that repeated BTX injections may be helpful when symptoms relapse.³⁷ These results are promising, but none of these studies were randomized or placebo-controlled. Thus, concrete conclusions regarding the utility of BTX in spastic esophageal motility disorders are not available at this time.

Gastroduodenal

Overview The pylorus is a thick, muscular ring separating the stomach from the duodenum both anatomically and physiologically.³⁸ Extrinsic innervation is provided by branches of the vagus nerve and by sympathetic fibers, whereas intrinsic innervation is supplied by the myenteric plexus of the stomach.³⁹ Baseline tone and phasic activity of the pylorus is primarily mediated by ACh, substance P, and enkephalins, whereas relaxation is largely the result of NO and vasoactive intestinal polypeptide.⁴⁰⁻⁴⁴

The rationale for injecting BTX into the pylorus for the treatment of gastroduodenal disorders arises from several lines of evidence: both baseline pyloric tone and phasic activity are greater in diabetic patients than in healthy volunteers^{45,46}; hyperglycemia induces phasic pyloric contractions in normal volunteers⁴⁷; in vitro studies using guinea pig pyloric muscle strips have demonstrated that BTX A decreases pyloric muscle contractions in a dose-dependent manner by inhibiting ACh release and directly inhibiting smooth muscle contractility⁴⁸; BTX inhibits the release of substance P from the myenteric plexus of the pylorus⁴⁹; and pyloric pressures, measured using a water-perfused Dent sleeve assembly, are reduced after BTX A injection.⁴⁶ These findings led to a number of clinical studies, which are described below.

The Pylorus Wiesel and colleagues described 2 patients who developed intractable postoperative gastric retention with recurrent nausea and vomiting.⁵⁰ Both patients had failed standard medical therapy. One patient had a

barium study that revealed a “tight” or “spastic” pylorus. Each patient was injected with 80 U total of BTX A into the pylorus (20 U × 4 quadrants). Each patient had resolution of symptoms, and 1 patient underwent a follow-up barium swallow examination that revealed free flow of barium through the pylorus. Neither patient, however, underwent gastric emptying scan (GES) or underwent antroduodenal manometry.

Gupta and Rao reported that abnormally prolonged, isolated pyloric pressure waves in a woman with type I diabetes were resolved after intrapyloric BTX A injection (200 U).⁵¹ Recurrent vomiting ceased, and persistent symptoms of nausea improved 1 week after injection and remained improved at 6-month follow-up.

Gastroparesis This disorder may be defined as the impaired transit of intraluminal contents from the stomach to the duodenum in the absence of mechanical obstruction. Typical symptoms include nausea, vomiting, early satiety, anorexia, weight loss, and abdominal pain. Gastroparesis is commonly seen in patients with diabetes, prior gastric surgery, collagen vascular disorders, anorexia, or pseudoobstruction. However, the etiology of gastroparesis remains undetermined in up to 50% of cases.⁵² A prior infectious illness, which is often unrecognized or not remembered, may be responsible for the development of idiopathic gastroparesis in many patients. The pathophysiology of gastroparesis includes impaired fundal tone, antral hypomotility, antroduodenal dyscoordination, gastric pacemaker dysrhythmias, and excessive inhibitory feedback from the small bowel to the stomach.⁵³ Patients with gastroparesis may have one or more of these pathophysiological abnormalities as the basis of their symptoms.

The medical treatment of gastroparesis usually employs a low-fat, low-residue diet and prokinetic agents such as erythromycin, metoclopramide, cisapride, and domperidone.⁵³ Unfortunately, these agents are often not available for general use (domperidone, cisapride), are associated with significant side effects (cisapride, metoclopramide), or are effective only in the acute setting (erythromycin). The lack of efficacy of these agents⁵⁴ may be due to the fact that they all act globally throughout the stomach, rather than on one specific region of the stomach. For example, it is quite possible that a patient with gastroparesis secondary to pylorospasm or antroduodenal dyscoordination might not improve with cisapride, as this drug has the potential to increase pyloric tone and further delay gastric emptying.⁵⁵

Diabetic Gastroparesis Several studies have focused on the utility of BTX injection in patients with diabetic gastroparesis. The first open-label trial of BTX injection in the pylorus involved 6 diabetic men (mean age=62 years;

years with diabetes >10) with symptoms of gastroparesis and evidence of delayed gastric emptying using a solid-phase GES.⁵⁶ In the trial, 100 U of BTX A was injected into the pylorus via 4 quadrant injections, a repeat solid-phase GES was performed at 48 hours and 6 weeks after injection, and symptoms were assessed at 2 and 6 weeks after injection. Using the amount of radio-labeled material emptied at 90 minutes as a marker, mean gastric emptying improved from 27.8% (baseline) to 49% (at 6 weeks; $P=.025$), whereas symptom scores (summary of nausea, vomiting, and bloating, using a 3-point scale) improved by 55% compared with baseline at both 2 and 6 weeks ($P=.025$). No patient suffered any adverse events from the injection. Although positive, these results must be interpreted with caution, as the study was small, not randomized, and not placebo-controlled.

Eight patients with diabetic gastroparesis who had failed standard therapy (mean age=41 years, mean years with diabetes=25.3 years) were treated with 200 U of BTX A injected into the pylorus in an open-label study.⁴⁶ Symptom scores (12 questions using a 3-point scale), standardized questionnaires (SF-36, SCL-90), solid-phase GES, laboratory studies (complete blood count, hemoglobin A1c, electrolytes, blood urea nitrogen, creatinine, glucose), and antropyloric manometry were performed prior to treatment. Symptoms were monitored at routine follow-up visits, and solid-phase GES and antropyloric manometry were repeated 1 week after injection (and compared to 8 healthy volunteers). No adverse events occurred during the study, and 7 of the 8 patients completed all phases of the study. Average symptom score declined from 27 to 12.1 ($P<.01$). The mean GES time (± 12) improved in all patients from 339 to 227 minutes ($P=.11$), and GES times improved significantly or normalized in 4 of the 8 patients. Six patients gained weight, and all patients noted a reduction in the amount of antiemetic medications they used. Antropyloric manometry demonstrated pylorospasm in all 8 patients (not present in any of the age- and sex-matched healthy volunteers), which was significantly reduced after BTX A injection. Similar to the study by Ezzeddine and associates,⁵⁶ this study is limited by the lack of a placebo group, as well as the use of a nonvalidated symptom scale.

In a retrospective review, Bromer and colleagues identified 63 patients (53 women, mean age=41.8 years) with symptoms of gastroparesis and delayed gastric emptying who had undergone BTX injection of the pylorus (100 or 200 U) over a 4-year period.⁵⁷ Thirty-seven patients (58.7%) had idiopathic gastroparesis, whereas 26 patients (41.3%) had diabetes and delayed gastric emptying. The authors reported that of all patients treated with BTX, 43% noted an improvement in symptoms, with a mean duration of response of 4.9 months in women and 3.5 months in men. No adverse events were reported. Vom-

iting as a major symptom was associated with a poor response to therapy, and men appeared to respond better than women. Although this study is important because it is the largest of its kind published to date, it is limited by its retrospective nature, the lack of a placebo group, the absence of a validated symptom score, the use of different doses of BTX A, and the lack of follow-up GES.

Idiopathic Gastroparesis Several trials have focused on the efficacy of intrapyloric BTX injection in patients with idiopathic gastroparesis, with conflicting results. The first study enrolled 10 women with idiopathic gastroparesis in a prospective open-label trial.⁵⁸ Symptom scores and 4-hour solid-phase GES times were assessed 4 weeks after intrapyloric injection with BTX A (80–100 U) and compared to baseline. The mean age of the patients was 41 years, with an average duration of symptoms of 4 years. Scintigraphic findings showed that the percentage of content remaining in the stomach at 4 hours decreased from 27% ($\pm 6\%$) to 14% ($\pm 4\%$; $P=.038$). Symptom scores decreased 38% from 15.3 (± 1.7) at baseline to 9.0 (± 1.9 ; $P=.006$), and the greatest improvements occurred with symptoms of epigastric fullness, epigastric discomfort, early satiety, and bloating. The improvement in symptom scores correlated reasonably well with the change in solid-phase GES times ($r=.580$; $P=.080$); however, no improvements were noted in liquid GES times. Although this pilot study is limited by its short follow-up period and the fact that it was not placebo-controlled, it confirmed the results of prior trials demonstrating the ease and safety of intrapyloric BTX A injection.

Twenty patients with gastroparesis (17 idiopathic) who had failed standard prokinetic therapy were enrolled in an open-label study involving 100 U of intrapyloric BTX A.⁵⁹ Liquid and solid-phase gastric emptying studies were measured at baseline and 4 weeks after treatment using breath tests with ^{14}C -octanoic acid (to measure solid-phase emptying) and ^{13}C -glycin (to measure liquid emptying). Symptoms were assessed at the time of GES using a 4-point scale to evaluate meal-induced symptoms. The mean age of the patients was 37 years, and 85% of the patients were women. One month after BTX injection, the solid-phase GES time improved from 204 (± 35) to 132 (± 16) minutes ($P=.04$), though liquid gastric emptying times did not improve. The cumulative meal-related symptom score decreased from 104 (± 17) to 74 (± 16) 1 month after injection ($P=.01$); however, only the individual scores of fullness ($P=.02$) and belching ($P<.005$) were statistically significant at 1 month after injection. In contrast to the study by Miller and coworkers,⁵⁸ no relationship was found between improvements in gastric emptying time and symptoms. Although this study had a short follow-up period and was not placebo-controlled, the addition of a meal-related symptom score is interest-

ing, as most patients with gastroparesis have significant symptoms in relation to meals.

The first randomized, placebo-controlled trial to evaluate the efficacy of BTX in patients with idiopathic gastroparesis was reported in 2007.⁶⁰ Twenty-three patients (5 men, mean age=45.2 years, 19 with idiopathic gastroparesis, mean duration of symptoms=6.2 years) were enrolled in a double-blind, placebo-controlled, crossover study. The Gastroparesis Cardinal Symptom Index (GCSI; 9 symptoms, score of 0–5), a validated symptom score, was used to measure symptoms at baseline and before each injection.⁶¹ As previously described, gastric emptying times using both liquids and solids were measured using a breath test and radio-labeled materials.⁵⁹ Patients were randomized in a blinded manner to receive either 100 U of intrapyloric BTX A or saline. One month after the initial injection, patients were crossed-over to receive the other treatment in a blinded manner. The authors reported that both the placebo group ($P=.01$) and the BTX group ($P<.05$) had an improvement in solid-phase gastric emptying after the initial injection (whether BTX or saline) when compared to baseline. However, when the data were pooled for both treatments, no difference was noted for solid GES time for BTX compared to placebo. In addition, for the group initially treated with saline, GES times did not improve after the second injection with BTX. Analysis of pooled data showed that postprandial symptoms of fullness and bloating improved significantly after BTX injection, though overall symptom scores, using the GCSI scale, did not differ between the placebo injection and the BTX injection. In summary, this trial confirms prior studies showing that BTX injection is safe and easy to perform, as no adverse events were reported. However, BTX was not significantly better than placebo, raising the questions of whether the symptom improvement reported in other trials represents a placebo effect and whether the improvement in gastric emptying simply represents regression to the mean. It is also possible, however, that small improvements were not noticed, given the small sample size, and that a longer follow-up period would be required to identify treatment benefits.

In another single-center, randomized, double-blind, placebo-controlled study, Friedenberg and colleagues assessed solid-phase gastric emptying and symptom scores 1 month after intrapyloric BTX A injection (200 U).⁶² The validated GCSI symptom score was used, and all patients had a score greater than 27, which meant that their symptoms of nausea, vomiting, and epigastric pressure were moderate-to-severe in nature. Thirty-two patients who had persistent symptoms despite medical therapy were randomized to 1 of 2 treatment groups: BTX A or saline. Six patients in the BTX group and 7 in the saline group had idiopathic gastroparesis, whereas

9 in each group had diabetic gastroparesis. The mean age of all patients was 41 years, and 80% of the patients were women. The primary endpoint for this study was a reduction in gastroparesis symptoms by 9 or more points (using the GCSI score) 1 month after treatment. Using this criteria, 56% of patients treated with placebo improved at 1 month compared with 37% treated with BTX A ($P=.29$). Gastric emptying 1 month after intrapyloric injection did improve more in the BTX A group ($P=.01$) than in the placebo group ($P=.62$) when compared to baseline, though the difference between the groups was not statistically significant ($P=.27$). Adverse events thought to be related to BTX A (headache) were not more prevalent in the BTX group than in the placebo group. In summary, intrapyloric BTX A injection was no better than placebo at improving symptoms of gastroparesis or accelerating gastric emptying. The lack of efficacy in this study may reflect the greater severity of symptoms, as defined by the GCSI score, and may also reflect the heterogeneous patient group (idiopathic or diabetic). Although the effect was not statistically significant, diabetics appeared to respond somewhat better than patients with idiopathic gastroparesis. This finding could reflect the presence of pylorospasm in patients with diabetic gastroparesis, which has not been studied in patients with idiopathic gastroparesis.

In summary, several open-label studies have shown the benefit of intrapyloric BTX A injection for relief of gastroparesis symptoms, though two recent small, double-blind, placebo-controlled trials have not (Table 1). These contradictory results have likely emerged for a variety of reasons, including differences in study design, differences in the doses of BTX A employed, inhomogeneous study populations, variations in follow-up length, and differences in types of GES and symptom scores employed. In addition, a critical question that must be answered is whether BTX A will be effective only in patients with documented pylorospasm. Large well-designed trials are needed before BTX A injection of the pylorus can routinely be recommended for patients with gastroparesis.

Anorectal Disorders

BTX has been used to treat a variety of anorectal disorders, including anal fissures, puborectalis syndrome, and postsurgical hemorrhoidectomy pain. Although frequently used, and in some conditions well-studied, the use of BTX A has not been approved by the FDA for the treatment of anorectal disorders.

Chronic Anal Fissure Injection of BTX into the anal sphincter has been shown to improve healing of chronic anal fissures. An important early study demonstrating the efficacy of BTX was published in 1998.⁶³ In this ran-

Table 1. Botulinum Toxin (BTX) for the Treatment of Gastroparesis

Study	Patient Population	Design	N	Dose of BTX used	Outcome Measures	Results
Ezzeddine, et al. ⁵⁶	Diabetic	Open-label	6	100 U	Solid-phase GES, symptoms	Symptoms and GES improved
Lacy, et al. ⁴⁶	Diabetic	Open-label	8	200 U	Solid-phase GES, symptoms	Symptoms, APM, and GES improved
Bromer, et al. ⁵⁷	IG & diabetic	Retrospective	63	100–200 U	Symptoms	45% of pts. had symptom improvement
Miller, et al. ⁵⁸	IG	Open-label	10	80–100 U	Symptoms, 4-hr GES	Symptoms and GES improved
Arts, et al. ⁵⁹	IG & diabetic	Open-label	20	100 U	Symptoms, liquid and solid-phase breath tests	Symptoms and solid-phase GES improved
Arts, et al. ⁶⁰	IG & diabetic	Double-blind, randomized, placebo-controlled	23	100 U	Validated symptoms score, breath tests	No difference between BTX and saline
Friedenberg, et al. ⁶²	IG & diabetic	Double-blind, randomized, placebo-controlled	32	200 U	Validated symptoms score, solid-phase GES	No difference between BTX and saline

APM=antropyloric manometry; GES=gastric emptying scan; IG=idiopathic gastroparesis.

domized placebo-controlled trial of 30 patients (control group: mean age=49 years, 13 men; treated group: mean age=38 years, 7 men) with chronic anal fissures, 11 of the 15 patients who received BTX (20 U) injection into the internal anal sphincter had resolution of their fissures at 2 months compared to 2 of the 15 patients in the control group who received saline injection.

In a different randomized controlled trial, BTX, using either the US formulation (30 U BTX) or the European formulation (90 U Dysport), was compared to nitroglycerin ointment (0.2%) for the treatment of chronic anal fissures. Fifty patients (mean age=42 years, 25 women) received BTX injection into the internal anal sphincter.⁶⁴ At 2 months postinjection, 46 of the 50 patients (92%) in the BTX group experienced resolution of their fissures compared to 35 patients (70%) in the nitroglycerin group ($P=.009$). Four patients required repeat BTX injection. In the BTX group, there were no relapses during the mean 16 months of follow-up. Three of the 50 patients experienced incontinence of flatus, which resolved spontaneously at 3 weeks postinjection.

BTX A has also been used successfully in patients with isosorbide dinitrate ointment-resistant chronic anal fissures. In a consecutive series of 100 patients (median age=45 years, range=20–79 years) with isosorbide dinitrate

ointment-resistant chronic anal fissures, patients were treated with an injection of 40–100 IU BTX A into the internal anal sphincter. At a median follow-up of 10 months (range=4–38 months), 77 of the 100 fissures (77%) had resolved. Repeated injection was required in 20 patients. Eleven patients ultimately experienced fissure recurrence, and 1 patient (1%) had temporary incontinence of flatus.⁶⁵

Finally, BTX A may have antinociceptive receptor effects independent of fissure resolution. One review of the literature found that symptomatic improvement occurred before the healing of the fissure (with reduction in pain within 1 week of therapy).⁶⁶ Furthermore, the review noted that at 3 months time, 3–25% of patients were pain-free despite persistence of the fissure. This antinociceptive effect has been noted in other painful conditions such as torticollis. This effect is also suspected to play a role in the reduction of posthemorrhoidectomy pain (which will be discussed later.)

If the initial BTX is ineffective or if fissures recur, repeated therapy with BTX may still be beneficial.⁶⁷ In patients who fail repeated BTX therapy, reasons for recurrent or nonhealing fissures, such as undiagnosed inflammatory bowel disease, should be considered. Additionally, it is important to consider surgical management of chronic

anal fissure in adults. In fact, a Cochrane review in 2006 found that surgery was superior to medical therapy, though it carried an increased risk of fecal incontinence.⁶⁸

Outlet-type Constipation Puborectalis syndrome is thought to be a behavioral disorder in which there is failure of relaxation, or even paradoxical contraction, of the puborectalis muscle during defecation. In a small study of only 4 patients (38–70 years of age, 3 men), BTX was injected into 2 sites on either side of the puborectalis muscle under the guidance of transrectal endoscopic ultrasonography.⁶⁹ These patients all experienced improvement in the frequency of spontaneous bowel movements from 0 to 6 per week, and laxatives were needed in only 1 patient. A more recent and larger study involving 24 patients (mean age=56 years, 14 women) showed similar improvement in symptoms and improvement in anorectal angle during straining on defecography.⁷⁰ At 4 weeks posttherapy, anorectal manometry showed decreased tone during straining from 96.2 to 42.5 mmHg ($P=.003$). It is important to note, however, that these studies were all open-label and without a placebo group.

Similarly, in patients with Parkinson's disease, outlet-type constipation has been attributed to focal dystonia of the pelvic floor and failure of the puborectalis muscle to relax. In an open-label study involving 18 patients (mean age=62 years, 14 men) with Parkinson's disease and outlet obstruction, there was symptomatic improvement in 10 patients with corresponding improvement in anorectal manometry and defecography,⁷¹ though there was no comparison to a placebo group.

Anterior Rectocele Due to Outlet Obstruction The pathogenesis of anterior rectoceles is unknown, though it has been suggested that some rectoceles may be caused by failure of the puborectalis muscle to relax. In an open-label study, a series of 14 women (mean age=55 years) with anterior rectoceles were treated with injection of BTX A, 30 U into 3 sites, 2 on either side of the puborectalis muscle and the third anteriorly in the external anal sphincter. This was performed under ultrasonographic guidance. Nine patients (64%) had symptom improvement.⁷² Initial rectocele depth of 4.3 (± 0.6) was reduced to 1.8 (± 0.5 ; $P<.05$). No relapse of symptoms was seen at 18 months of mean follow-up in any of the patients. At 1-year follow-up, none of the patients reported using digital assistance to evacuate stool and none had evidence of a rectocele on digital examination, though 4 of the 14 study participants had a rectocele identified by defecography.

Posthemorrhoidectomy Pain Hemorrhoidectomy is considered a safe and effective procedure for the treatment of severe hemorrhoids, though postoperative pain is a

common complication. After hemorrhoidectomy, the maximum resting pressure of the anal canal significantly increases and is thought to play an important role in postoperative pain.⁷³ BTX, when compared to placebo, has been shown to decrease postoperative pain both at rest and with defecation.⁷⁴ In a small study of 30 patients (mean age=40 years, men=women) with third- and fourth-degree hemorrhoids, a comparison of BTX (20 U) to glyceryl trinitrate (200 mg) found that the BTX group had significant reductions in postoperative pain at rest compared to the glyceryl trinitrate group ($P=.01$). There were no differences in pain with defecation or in wound healing between the two groups.⁷⁴ Here again, the possible antinociceptive effects of BTX may also play a role in measured pain relief.

Biliary Disorders

Sphincter of Oddi dysfunction (SOD) is a syndrome of chronic biliary pain or pancreatitis due to functional obstruction at the level of the sphincter of Oddi. There are 3 types of patients, according to the Milwaukee classification scheme: type I patients, who have pain as well as abnormal liver function tests and a dilated common bile duct; type II patients, who have pain and only one of the above objective findings; and type III patients, who have only biliary pain.⁷⁵ The diagnostic gold standard for the identification of SOD is biliary manometry; however, it is not widely available and carries the risk of postprocedure pancreatitis. As a result, manometry is not recommended prior to sphincterotomy for type I patients, though it is recommended for type II patients. Manometry may not accurately predict response to sphincterotomy in type III patients and, thus, is not generally recommended.

At present, there appear to be 3 potential uses of BTX in SOD: diagnostically, to identify which SOD patients might respond to sphincterotomy; prophylactically, to prevent post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis following sphincterotomy in SOD patients; and therapeutically, to temporarily relieve symptoms. With regard to its diagnostic utility, several uncontrolled case series have demonstrated that BTX injections have a high positive predictive value in identifying patients whose symptoms may improve after sphincterotomy.^{76,77} In 1998, Wehrmann and colleagues performed a prospective study in which 22 patients who had undergone cholecystectomy and who had manometrically confirmed type III SOD received 100 U BTX into the papilla of Vater via a single injection.⁷⁶ Twelve patients experienced symptomatic relief, with documented relief of sphincter hypertension in 11 patients. These 11 patients subsequently underwent sphincterotomy and remained symptom-free at 15 months. Of the 10 patients who did not respond to BTX, only 2 patients had symptom relief

following sphincterotomy ($P < .01$). In a later study, 15 patients (mean age=38 years; 9 women) with manometric findings consistent with SOD underwent BTX injection (100 U) into the major papilla. At 3 months follow-up, 12 of the 15 patients remained asymptomatic; however, 11 of the 12 patients relapsed by 6 months and underwent sphincterotomy. All patients remained in clinical remission at 15 months.⁷⁷

BTX has also been used prophylactically to reduce the risk of post-ERCP pancreatitis in SOD patients. In a study of 26 patients with documented elevated SOD pressures, 12 received BTX (2 injections of 25 U into the pancreatic sphincter) and 14 received a sham injection (saline injected into the duodenal lumen). Six patients (43%) developed post-ERCP pancreatitis as opposed to 3 (25%) in the BTX group ($P = .34$).⁷⁸

Lastly, BTX has been used therapeutically to provide short-term symptom relief. Symptomatic relief is thought to be related to a reduction in sphincter hypertension, which was first documented in a small case report in 1998⁷⁹ and supported by the larger above-mentioned studies. All three applications require randomized controlled trials to better delineate the role of BTX in relation to diagnostic manometry, prophylactic pancreatic stent placement, and therapeutic sphincterotomy.

Other Potential Uses

Obesity

The preliminary results obtained from the gastroparesis studies described above encouraged researchers to investigate whether BTX could slow gastric emptying and, thereby, lead to early satiety and weight loss, if injected into the antrum or body of the stomach. The first study to evaluate the utility of BTX in the treatment of obesity was performed in nonobese Wistar rats.⁸⁰ This prospective trial, which measured daily food intake over 7 weeks and body weight over 10 weeks, consisted of 3 groups of rats: a control group (no treatment; $n=5$), a laparotomy group with antral BTX A injection (20 U; $n=14$), and a laparotomy group with saline antral injection ($n=14$). This study found that BTX A injection led to a significant reduction in both food intake ($P < .05$) and weight ($P < .001$) compared with the sham injection group.

A small, open-label, prospective trial enrolled 8 patients (50% women; median age=46 years) with severe obesity (median body mass index [BMI]=47.1 kg/m²) to assess the efficacy of antral BTX A injection for weight loss.⁸¹ After BTX injection into the antrum (500 U total), all 8 patients lost weight, with a median weight loss of 2.6 kg at 1 month ($P < .05$). Three patients noted further weight loss at 4 months. Weight loss was not related to changes in hunger, satiety, plasma ghrelin levels, or leptin levels. Although interesting, this study is hampered by its

small sample size, the lack of a placebo group, and the use of nonvalidated symptom questionnaires.

A larger, double-blind, randomized, controlled trial of morbidly obese men (BMI >35 kg/m²) also found that BTX A injection of the antrum and fundus reduces food intake and weight.⁸² Weight, satiety score (determined by a visual analog scale), gastric emptying (assessed by ¹³C-octanoic acid), and nutrient drink test were examined prior to endoscopic treatment. Twenty-four patients were randomized to receive 200 U of BTX A (12 injections; 4 each into the antrum, upper body, and fundus) or normal saline during upper endoscopy. All patients then initiated a 1,200 kcal liquid diet for the 8-week study period. At the end of the study, patients treated with BTX A had a greater reduction in weight than patients treated with saline (11 kg vs 5.7 kg; $P < .0006$). Satiety was increased in both groups compared to baseline and was greater in the BTX A group from week 2 onward ($P < .01$). The maximal gastric capacity for the nutrient drink test was reduced in both groups compared to baseline, but more so in the BTX group, and this was significantly greater than placebo ($P < .001$). Lastly, gastric emptying was slightly delayed (18 minutes) in patients treated with BTX A compared to saline ($P < .05$), though this was not clinically significant. This study is noteworthy because it is the largest of its kind published to date and highlights the fact that large treatment groups are required to identify a treatment effect. In addition, BTX A injection was performed in the antrum, body, and fundus; other studies have concentrated on the antrum, and it is possible that a larger area of the stomach must be injected in order to maximize the effects of weight loss.

In contrast to these studies, a number of trials have not been able to demonstrate any significant benefit using BTX for the treatment of obesity. An open-label prospective trial of 12 obese patients (BMI >30 kg/m²) evaluated gastric emptying and weight loss after BTX A injection into the antrum.⁸³ Eight women and 4 men participated in this study, which had a median age of 29 years. All patients tolerated the injection well (8 sites, 100 U total), and 5 patients reported new symptoms of early satiety after BTX injection. Although BTX was well-tolerated, weight remained similar to baseline at 4- and 12-week follow-up visits, at which intervals GES times were no different from baseline ($P > .05$).

In an attempt to better understand the role of dose and the location of BTX injection for the treatment of obesity, Junior and associates performed an open-label study in 12 obese patients.⁸⁴ Patients were randomized to 1 of the following treatment groups: 200 U of BTX A injected at either 8 or 16 antral sites; or 300 U of BTX injected at either 16 or 24 antral sites. Body weight and gastric emptying using a ¹³C-octanoic breath test were measured prior to endoscopic treatment and at intervals during the

12-week follow-up period. Although all patients noted symptoms of early satiety after the treatment, no changes in weight or gastric emptying were reported.

The efficacy of BTX A for weight reduction was further evaluated in a randomized, placebo-controlled, double-blind study comparing 2 different doses of BTX A to placebo.⁸⁵ Eighteen morbidly obese patients (mean BMI=46.6 kg/m², 50% women) were randomized to receive antral injections of 133 U of BTX, 200 U of BTX A, or saline (8 injection sites). A solid-phase GES was performed 10 days after injection and compared to baseline. Both weight and a visual analog scale (designed to assess satisfaction with food intake) were measured 5 weeks after injection and compared with baseline. Four patients were excluded from the study due to abnormal endoscopic findings. All patients tolerated BTX injection well without any complications. No difference was noted in gastric emptying times after treatment. Patients treated with BTX A lost more weight than those treated with placebo: 7.4 kg in the BTX 133 U group versus 5.8 kg in the BTX 200 U group, though these findings were not statistically significant when compared to the saline injection group.

Finally, a randomized, double-blind, placebo-controlled trial of 10 women with class I obesity (BMI 30–35 kg/m²) found that BTX A injection (200 U) was no better than placebo (saline) at causing weight loss over a 6-month period.⁸⁶ No significant differences were noted with regard to sensations of satiety.

In summary, BTX A may prove to be a treatment option for patients with morbid obesity. The discordant results noted above highlight the need for large, randomized, controlled trials evaluating both the location and dose of BTX A injection. Standardized questionnaires will be required to assess satiety and hunger, and both nutrient drink tests and GES tests should be used to help identify changes in gastric physiology.

Proctalgia Fugax

Proctalgia fugax is characterized by the unpredictable, sudden onset of sharp, stabbing, cramping rectal pain. It affects approximately 3–14% of adults, most of whom have 5–6 episodes per year. Episodes last from seconds to minutes and resolve spontaneously. The pain is thought to develop because of spasm in the anal canal, though elevated anal canal pressures have been identified in some patients. Medical therapy, including Sitz baths, enemas, anti-inflammatory agents, smooth-muscle antispasmodics, and nitrates, are typically ineffective. BTX injection of the anal canal has not been performed in a controlled trial for the treatment of proctalgia fugax, but appears to be reasonable physiologically and warrants investigation.

Risks and Adverse Reactions

Overall, the use of BTX A appears to be safe and effective in the treatment of multiple GI disorders. Its primary limiting factor appears to be the need for repeated doses, in the setting of an ineffective initial response or a short duration of response.

In general, adverse reactions occur within the first week after injection (due to clinical pharmacology). Potential adverse reactions are local reactions at the site of injection (including local pain and tenderness), rash, and hematoma. Since the marketing of BTX, other adverse reactions have been reported; however, a causal relationship has not been established. These adverse reactions include skin rash (erythema multiforme, urticaria, psoriasiform rash), pruritus, and allergic reaction. Other reactions depend upon the site of reaction, such as ptosis in patients treated for blepharospasm. Temporary incontinence of flatus or stool has been reported in the treatment of chronic anal fissure (approximately 7%). In all patients, these adverse reactions typically resolve spontaneously at 3 weeks. Mild pancreatitis has been associated with intrasphincteric injection of BTX into the minor papilla.

Development of neutralizing antibodies has also been described.¹⁰ The critical factors resulting in antibody formation are unknown, but there may be an increased risk of antibody formation with higher and/or more frequent doses. To minimize the risk of antibody formation, use of the lowest dose at the longest feasible interval is advised. If antibodies to BTX A develop, BTX B could be tried, as there is no cross-reactivity between the 2 toxin types.¹⁰⁻¹²

Conclusion

Over the last century, the image of BTX has been transformed from a feared poison to a safe medication dispensed in the outpatient setting. Gastroenterologists routinely use BTX to treat a variety of GI disorders because it is safe, easy to use, and it improves symptoms in many patients who have failed conventional therapies. Contrary to what is written in the lay press, however, BTX is not a panacea for the treatment of all medical conditions, as illustrated by the conflicting data from studies in patients with gastroparesis. An important theme from all of the studies described in this review, however, is that injection therapy does have a role in our therapeutic armamentarium, as it provides medication directly to the area that needs it, rather than distributing it throughout the body. Not only can this approach improve symptoms; it can also minimize side effects associated with the use of systemic medications. The positive outcomes evidenced in many of the BTX trials should stimulate further research into other injectable therapies, which may include depot

injections of BTX, long-lasting nitric oxide donors, and antagonists of substance P.

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