Botulinum Toxin A Use in the Gastrointestinal Tract: A Reappraisal After Three Decades

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Abstract: The discovery of botulinum toxin A (BTX)'s therapeutic properties has led to studies evaluating its usefulness in multiple medical disorders. Its use in the gastrointestinal (GI) tract has been studied for 30 years. Multiple databases, including PubMed, AccessMedicine, ClinicalKey, Cochrane Library, Embase, and Medline, were used to review research from case series to randomized controlled trials on BTX use in the GI tract. This article reviews the current literature on the efficacy of BTX and the strength of recommendations for or against its use in various disorders, including cricopharyngeal dysphagia, achalasia, nonachalasia motility disorders, gastroparesis, obesity, sphincter of Oddi disorders, chronic anal fissure, chronic idiopathic anal pain, and anismus. The appeal of BTX comes from its simplicity of administration, good safety profile, and reliability in decreasing muscular tone. However, there are several drawbacks that limit its use, including the lack of long-term efficacy and/or limited data in many GI disorders.

Keywords
Botulinum toxin A, achalasia, gastroparesis, endoscopy, obesity, sphincter of Oddi disorders, esophagus, fissure

Botulinum toxin A (BTX) is produced by *Clostridium botulinum* and is a neurotoxin that causes flaccid paralysis by inhibiting the release of acetylcholine from axonal endings at the neuromuscular junction.[1] Since its first clinical use in 1973, the discovery of BTX as a therapeutic option has led to several advances in treating a multitude of neuromuscular, urologic, gastrointestinal (GI), and dermatologic disorders, among others.[2] The goal of injection is to relax the targeted muscles, and experimentation in the GI tract has been underway since at least 1988 in the treatment of anismus for idiopathic constipation.[3] Over the past 30 years, research on BTX use in the GI tract for a variety of disorders has continued to grow, particularly in areas of motility and spastic disorders such as achalasia, diffuse esophageal spasm (DES), gastroparesis, sphincter of Oddi disorders, chronic anal fissures (CAFs), and pelvic floor dysfunctions. It has also garnered much interest in disorders

Table 1. Botulinum Toxin A Use for Cricopharyngeal Dysphagia

Study	Study Design	Sample Size	Dose (units)	Patients Improved	Type of Intervention	Causes of Cricopharyngeal Dysphagia	Complications
Schneider et al[17]	Case series	7	80-120	5/7 (71%)	EGD	Stroke, CN palsies, supraglottic/oropharyngeal cancer, reflux	None
Blitzer and Brin[16]	Case series	6	10	6/6 (100%)	Percutaneous intervention	CVA, partial pharyngectomy, small Zenker diverticulum	None
Alberty et al[1]	Prospective clinical trial	10	30	10/10 (100%)	EGD	CVA, idiopathic polymyositis	None
Shaw and Searl[9]	Case series	12	25-50	10/12 (83%)	EGD, open technique	Progressive neuropathy, oculopharyngeal dysphagia, skull base tumor resection, total laryngectomy, CVA, partial pharyngectomy, CNS neuropathy	Pharyngeal tear, worsening dysphagia
Haapaniemi et al[4]	Case series	4	14-50	3/4 (75%)	EGD	Brain stem stroke, inclusion body myositis, peripheral motor neuropathy, CVA	None
Liu et al[18]	Case series	2	100	2/2 (100%)	EGD	Inclusion body myositis	None
Krause et al[6]	Case report	1	180 150	1/1 (100%) 0/1 (0%)	EGD	Spasticity secondary to SAH	None
Alfonsi et al[7]	Prospective observational trial	34	15	17/34 (50%)	EMG-guided transcutaneous approach	MS, multiple system atrophy, Parkinson disease, progressive supranuclear palsy, ataxia-telangiectasia	None
Jeong et al[15]	Retrospective study	14	100	11/14 (79%)	EGD	Cricopharyngeal muscle dysfunction, neurologic disease	Temporary worsening of dysphagia/dysphonia

CN, cranial nerve; CNS, central nervous system; CVA, cerebral vascular accident; EGD, esophagogastroduodenoscopy; EMG, electromyography; MS, multiple sclerosis; SAH, subarachnoid hemorrhage.

such as obesity. This article reviews the current literature on the use of BTX in different regions of the GI tract.

Cricopharyngeal Dysphagia

Many neurologic disorders can cause dysfunction of the upper esophageal sphincter (UES) by impairing cricopharyngeal muscle relaxation during swallowing, which can lead to dysphagia and possible aspiration. BTX has been shown to have efficacy in treating cricopharyngeal dysphagia in several small case series; however, large randomized controlled trials (RCTs) are still lacking.[1,4-8] The endoscopic technique uses a standard adult flexible upper endoscope with a 5-mm sclerotherapy needle to deliver 3 to 4 injections of BTX 25 units (U)/mL or more into the cricopharyngeus.[9] However, a variety of other techniques have been used, including rigid endoscopy with electromyography (EMG) as well as an open technique with differing doses (onabotulinumtoxinA [Botox, Allergan] 10-50 U).[10,11] Some researchers believe that reflux must be well controlled before injection to rule out mimicry of a primary disorder and to avoid postinjection laryngeal complications caused by a weakening of the UES.[10,12-14]

Using BTX in cricopharyngeal dysphagia was intended to be an alternative to myotomy, as BTX appears to have a lower risk of complications and decent success. Table 1 summarizes multiple small-scale studies involving a variety of techniques.[1,4,6,7,9,15-18] Although BTX appears to be successful in this setting, variation in selected patients and techniques, small sample sizes, and lack of controls make it difficult to compare these studies. Thus, more research is needed.

A comprehensive systematic review published in 2016 examined more than 500 studies on the use of myotomy, BTX, and dilation in cricopharyngeal dysphagia. Logistic regression analysis of patient-weighted averages found that the success rate of BTX injection was 69%, but the success rate of myotomy was higher (78%; P=.042). The success rate of dilation was not statistically different from that of myotomy or BTX (P values of .37 and .42, respectively).[19]

Ultimately, BTX injections can be considered as an alternative to surgical myotomy in patients who are not optimal surgical candidates or who seek only temporary

relief of symptoms. BTX can also be used as a potential diagnostic test to predict response to surgical myotomy.[1,16,20,21] Alberty and colleagues believed that if patients had good clinical response and significant improvement on video fluoroscopic swallow study, they would likely benefit from repeat BTX injections or cricopharyngeal myotomy.[1] However, if there was no radiographic or clinical improvement, a stricture would be suspected and surgery considered.[1,10] Patients with multilevel dysphagia in whom surgical myotomy may be more detrimental may also be good candidates for BTX injection for treatment of cricopharyngeal dysphagia.[1,16,20,21]

Achalasia

Achalasia is a motility disorder of the esophagus in which there is a lack of relaxation at the esophagogastric junction and a lack of distal esophageal peristalsis. These consequences occur because of progressive degeneration of inhibitory neurons in the myenteric plexus in the esophagus, which leads to unopposed cholinergic muscle excitation. BTX works by blocking the release of acetylcholine from nerve endings to attenuate muscle excitation and reduce spasticity. Treatments for achalasia include surgical myotomy, peroral endoscopic myotomy (POEM), endoscopic pneumatic dilation (PD), and BTX injection.[22]

Although surgical myotomy is a durable option, it is associated with a higher likelihood of complications in patients who are high-risk surgical candidates. POEM is also durable but can be associated with iatrogenic gastroesophageal reflux disease.[23] PD has shown to be cost-effective, although it is less durable than POEM or Heller myotomy (HM), and has a small risk of causing esophageal perforation.[11,24,25] In patients with achalasia who are not ideal candidates for invasive procedures, BTX injections can be a viable option, particularly for type 2 achalasia. It was less effective in types 1 and 3 achalasia.[25,26]

Some of the earliest studies of BTX in achalasia were performed in the 1990s after preliminary testing on piglets.[27,28] The initial evaluation compared BTX injections with placebo injections of saline with a protocol to inject 80 U into 4 quadrants above the Z-line. Since then, a variety of techniques have been used for BTX injection in achalasia, including injections into 4 quadrants at 2 different levels in the lower esophageal sphincter (LES) region and below the gastroesophageal junction, endoscopic ultrasound–guided injections, and manometry-guided injections.[29-32] Injections are aimed into the muscular layer, but even patients who received injections in the submucosa showed significant symptomatic improvement, particularly in Chagas disease and achalasia over a period of 6 months.[33]

Optimal dosage of BTX with the lowest amount of relapse was found to be 100 U, according to a large multicenter randomized trial.[30] Multiple trials have looked at BTX injections in relation with placebo and alternative therapies, such as PD, HM, or a combination (see eTable 1 at www.gastroenterologyandhepatology.net).[29,30,32-42] Many of these studies showed that, in the short term, BTX can have equitable outcomes in comparison with other modalities with a lower incidence of complications; however, BTX has a higher rate of relapse in symptoms, and PD, HM, and POEM have more long-lasting efficacy.

Although BTX is safe and minimally invasive, it has several drawbacks. Although initial response can be excellent (~75%), only two-thirds of patients have sustained response at 6 months, with 60% of patients having recurrent dysphagia at 1 year and 80% at 2 years.[34,43,44] Another drawback is that BTX injection can cause submucosal fibrosis, which may make subsequent definitive therapy more difficult.[45] However, statistically, this did not affect overall outcomes in patients who received injections prior to HM or POEM.[40] BTX pretreatment prior to PD showed some benefit vs PD alone in 1 trial (69% vs 50%), but was not statistically significant (P=.07).[41]

Patients older than 50 years have higher response rates to BTX injections compared with younger patients for unclear reasons (82% vs 43%, respectively).[11] In a study of 33 elderly patients with achalasia (ages 81-94 years), BTX 100 U was injected into the LES; 78% were responders at 1 year, and 54% were considered responders at 2 years. Thus, in this age range, BTX can be a safe and effective alternative that yields a good quality of life in a large portion of patients without risks of major complications.[46] In patients who failed prior PD or HM, BTX injections resulted in improvement in 75% of patients. Although the duration of symptom relief was shorter, repeat injections of 100 U into the LES increased remission time.[42]

Overall, in achalasia, BTX is recommended for patients who are poor medical candidates for definitive treatment (eg, patients who are elderly, with multiple comorbidities, previous therapeutic failure) or as a transient treatment for very acute cases (eg, total outlet obstruction).[25] BTX can help predict who may respond well to alternative treatments such as PD or HM, but when used synergistically with other therapies, it does not increase remission time significantly.[39] It is also not effective in type 3 achalasia.[36]

Nonachalasia Motility Disorders

The use of BTX has been explored in nonachalasia motility disorders such as DES, hypertensive peristalsis (previously known as nutcracker esophagus), and isolated

Table 2. BTX Use for Gastroparesis

Study	Patient Population	Study Design	N	Dose (units)	Follow-up	Outcome Measures	Results
Ezzeddine et al[58]	DG	Open-label trial	6	100	6 weeks	Solid-phase GES, symptoms	Mean gastric emptying improved by 52% with a 55% improvement in symptoms at 6 weeks
Miller et al[62]	IG	Open-label trial	10	80-100	4 weeks	Symptoms, GES by scintigraphy	38% reduction in symptoms at 4 weeks, which correlated with increased gastric emptying in 70% of patients
Lacy et al[59]	DG	Open-label trial	8	200	12 weeks	Solid-phase GES, symptoms, change in weight	>50% reduction in symptoms and 4/7 patients who completed the trial had improvement in the solid phase. 6/7 patients gained weight, and prokinetic drug use was reduced in 50% of patients
Bromer et al[60]	IG and DG	Retrospective study	63	100-200	NA	Symptoms	43% of patients had improvement in symptoms, and the duration of response was 5.1 months. However, no control group, validated symptom score, or GES was used
Arts et al[63]	IG and DG	Open-label trial	20	100	4 weeks	Symptoms, GES by scintigraphy	Significant improvement in symptoms and solid-phase GES
Arts et al[64]	IG and DG	Double-blind, randomized, placebo-controlled, crossover trial	23	100	4 + 4 weeks	Validated symptom score, C^{13} breath tests	Not superior to placebo
Friedenberg et al[65]	IG and DG	Double-blind, randomized, placebo-controlled trial	32	200	4 weeks	Validated symptom score, solid-phase GES	Not superior to placebo
Coleski et al[66]	IG and DG	Retrospective study	179	100-200	NA	Symptoms	Significant improvement
Rameshshanker et al[61]	IG and DG	Retrospective study	21	200	2 years	Symptoms	62% of patients responded to treatment, with a mean response duration of 4.2 months. Response to BTX therapy was better in DG patients compared with IG patients
Rodriguez et al[67]	IG	Retrospective study	47	100	NA	Symptom score	Significant improvement

BTX, botulinum toxin A; DG, diabetic gastroparesis; GES, gastric emptying study; IG, idiopathic gastroparesis; NA, not available.

hypertensive LES, as the pathophysiology of these disorders is thought to develop secondary to an imbalance in tissue levels of acetylcholine and nitric oxide. Although some patients with DES and hypertensive peristalsis have symptomatic improvement with BTX injection, this is not always associated with changes on high-resolution manometry. In 2013, a prospective controlled trial of 22 patients with DES or hypertensive peristalsis compared BTX injection (100 U) vs placebo for improvements in dysphagia and noncardiac chest pain. The BTX group had significant improvement with sustained results in 50% of patients at 1-year follow-up, compared with the placebo group.[47]

In other studies, BTX injections showed improvement in dysphagia but not in heartburn or chest pain. There has been variable response with esophagogastric

junction outlet obstruction and noncardiac chest pain in small retrospective studies.[48] Overall, there appears to be a discordance between manometric findings and symptom improvement, in which improvement in both does not always coincide. This raises the question whether manometric findings can be used as a diagnostic or outcome measure in studying response to these therapies.[49]

Some case reports describe the benefits of BTX injections in the management of hypertensive LES.[44,50] An open-label trial of 29 patients showed a 50% reduction in noncardiac and nonreflux chest pain in 75% of patients for an average of 7.3 months.[51] In a clinical trial evaluating the use of BTX in patients with DES (n= 9), BTX 100 U was injected into multiple sites along the esophagus, including contraction rings. At 1 month, 8 of 9 patients had significant improvement in symptoms. At 2 years, 4 patients required subsequent injections.[52] These findings are promising; however, they need to be substantiated with larger RCTs.

Use of BTX in esophageal strictures is limited in the literature. However, a 2016 RCT of 67 patients evaluated BTX injections as a prophylactic way of preventing esophageal strictures after endoscopic submucosal dissection (ESD) of esophageal squamous cell carcinoma. BTX significantly reduced the development of strictures compared with ESD alone (6.1% vs 32.4%, respectively; $P<.05$). Thus, BTX injections may be effective in preventing post-ESD esophageal strictures.[53]

Gastroparesis

Gastroparesis is characterized by impaired gastric emptying into the duodenum in the absence of gastric outlet obstruction. Classifications include idiopathic gastroparesis (IG), diabetic gastroparesis (DG), and postsurgical states. Multiple mechanisms have been theorized, including muscular, neural, or humoral dysfunctions causing gastric pacemaker abnormalities; excessive inhibitory feedback from the small bowel; decreased fundal tone; antrum hypomobility; loss of interstitial cells of Cajal; myenteric plexus degeneration; and pylorospasm.[54-56] Injection of BTX into the pylorus was hypothesized as a way to improve gastric emptying.

Early open-label trials showed a significant reduction in symptoms in patients with DG and improvements in gastric emptying at varying intervals from 4 to 12 weeks. However, these trials tended to be low-powered and lacked randomization or control groups.[57-63] In 2007 and 2008, 2 randomized, double-blinded, placebo-controlled trials compared BTX injections with placebo saline injections and showed no statistical significance in the difference between the 2 groups in symptom improvement or solid-phase gastric emptying time. Improvements in gastric emptying time did not always correlate with symptom response.[64,65] Criticism of these trials includes having a small sample size (54 total patients) and heterogeneity in the gastroparesis population (mixture of IG and DG patients). Table 2 shows different trials evaluating BTX in gastroparesis.[58-67]

Studies have attempted to identify which subgroups of gastroparesis patients may be more responsive to intrapyloric BTX injections. A large retrospective analysis by Coleski and colleagues consisted of 179 patients who received intrapyloric BTX injections for gastroparesis over a 7-year period (DG, n=81; IG, n=76; BTX dose, 100-200 U).[66] More than half (51.4%) had symptom relief and weight improvement, whereas 32% had no benefit. Factors for better response included higher doses of injection, female sex, age less than 50 years, and etiologies not involving diabetes or surgery ($P<.05$). Response to repeat injections (87 total) was similar between patients who responded to the first injection and those who did not.[66] In 2017, Wellington and colleagues evaluated 33 gastroparesis patients with a suspected etiology of pylorospasms with normal gastric myoelectric activity.[68] BTX 100 U was injected intrapylorically, and symptomatic improvement was seen in 78% of patients ($P<.04$).[68] This could suggest that there is a subset of gastroparesis patients that may respond well to BTX injections, but further studies are needed.

Based on the 2 randomized trials available, the current American College of Gastroenterology guidelines recommend against the use of BTX injections for gastroparesis.[69] In practice, BTX injections may still be attempted at some facilities for refractory gastroparesis owing to a good safety profile.[70]

Obesity

It is hypothesized that BTX injection into the gastric antrum can relax gastric smooth muscle, thereby delaying propulsion of food into the duodenum, which leads to early satiety and thus reduces dietary intake and causes weight loss. Initial animal research showed significant weight loss ($P<.001$) and reduced food intake ($P<.05$) in rats who received BTX injection vs saline injection or no intervention over 7 weeks.[71]

One of the first pilot studies, in 2005, was a small, open-label, prospective trial of 8 patients (median body mass index [BMI] 47) who received gastric antral BTX injections (total 500 U) for weight loss. At 1-month follow-up, all patients lost weight, with a median weight loss of 2.6 kg and 3 patients continuing to lose weight 4 months after injection.[72] However, in the same year, a study on endoscopy-guided gastric antral BTX injections in 12 obese patients found no significant changes

in body weight or gastric emptying time in comparison with baseline values.[73] Two small, open-label, prospective studies of 10 to 12 obese patients found that those who received BTX injections had early satiety, but there was no significant reduction in weight loss or gastric emptying at 12 to 16 weeks.[74,75]

Since then, multiple RCTs have had mixed results. Studies have evaluated injection of BTX in varying locations of the stomach (ie, gastric angulus, antrum, or a combination of antrum and fundus) at differing doses (100-500 U) vs placebo. Many RCTs evaluating injection into the antrum or angulus found weight loss to be comparable between the BTX and placebo groups.[72-78] RCTs that have shown statistically significant weight loss have injected both the antrum and fundus. A double-blinded placebo RCT that showed the most statistically significant weight loss in obese patients was one that injected both the antrum and fundus. The trial included 24 morbidly obese patients and injected BTX 200 U or placebo into the antrum and fundus of the stomach. At 8 weeks, all patients in the BTX group had a statistically significant amount of weight loss (11 kg vs 5.7 kg; $P<.0006$) and a decrease in BMI (4 vs 2; $P<.001$) compared with the placebo group.[79] A randomized trial in 2012 evaluated BTX injection (200 U vs 300 U) into the antrum and fundus of 20 obese patients and found statistically significant weight loss, decreased triglyceride levels, and fasting ghrelin levels with longer gastric emptying times in both treatment groups at 12 weeks.[80]

In summary, the limited number of studies investigating the effects of BTX on weight loss in obese patients have at best shown equivocal results. The variability may be owing to small sample sizes and differences in location of injection, dosing, or operator skill. A meta-analysis of 6 studies concluded that BTX interventions had no benefit in terms of reduction in weight or BMI in obese patients; however, the meta-analysis did not consider the injection site as an important variable.[81] Many physicians have advocated for trials investigating BTX injections into the fundus because the studies reporting weight loss included it as a target site. Injection into the fundus could reduce gastric emptying and gastric accommodation, thereby increasing early satiety and decreasing oral intake. A higher-powered, randomized, double-blind, controlled trial is needed to evaluate this possibility.[82] With no apparent serious adverse effects related to its use, BTX still appears to be an attractive option to some doctors, but currently cannot be routinely recommended.

Sphincter of Oddi Disorders

The sphincter of Oddi is a ring of muscle that surrounds the distal end of the biliary and pancreatic ducts at the convergence prior to its emptying into the duodenum. Sphincter of Oddi dysfunction (SOD) is characterized by chronic biliary pain or pancreatitis owing to functional obstruction at the level of the sphincter of Oddi. According to the Rome IV criteria, there are 2 subtypes: functional biliary sphincter of Oddi disorder and functional pancreatic sphincter of Oddi disorder. In functional biliary sphincter of Oddi disorder, there is biliary pain associated with either elevated liver enzymes or a dilated bile duct (not both) and there are no biliary stones or structural abnormalities. In functional pancreatic sphincter of Oddi disorder, there must be recurrent episodes of pancreatitis, exclusion of other causes of pancreatitis, negative endoscopic ultrasound findings, and abnormal sphincter manometry. Endoscopic sphincterotomy is the standard of treatment but is considered a high-risk procedure that is not consistently effective. Thus, BTX, hypothesized to be a safer alternative, has been evaluated to see whether sustained response can be achieved.[83] Additionally, the role of BTX in predicting response to sphincterotomy has been evaluated.

Currently, there are a few potential uses of BTX in SOD. The first research on BTX in SOD examined whether it could predict which of 2 patients would respond to sphincterotomy.[84] Several uncontrolled case series or studies have since demonstrated that BTX injections may have a high positive predictive value in identifying patients who may improve after sphincterotomy.[85-87] In 1998, a larger study of 22 patients looked at BTX's effectiveness in type III SOD (using previous Milwaukee criteria: manometric basal sphincter pressures >40 mm Hg without laboratory or structural abnormalities). A single injection of BTX 100 U was inserted at the sphincter of Oddi, and 55% of patients responded to treatment with 92% remaining asymptomatic at 6 months. Eleven of 12 patients who had a recurrence of symptoms were treated with sphincterotomy and had long-term resolution of symptoms at 15 months. Of the 10 patients who did not respond to initial BTX injections, 5 had normal sphincter pressures and did not respond to sphincterotomy, whereas only 2 of the 5 with sustained sphincter hypertension benefited from subsequent sphincterotomy ($P<.01$).[85] However, patients with SOD who underwent biliary sphincterotomy had a higher risk of developing post–endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis thought to be secondary to residual pancreatic sphincter hypertension. A study in 2004 looked at BTX injection vs sham injection into the pancreatic sphincter of patients after biliary sphincterotomy and found some reduction in postprocedure pancreatitis; however, it was not statistically significant ($P=.34$).[88] Although these data may support a proof of concept for BTX, type III SOD is no

longer a recognized entity for which ERCP is indicated, according to the EPISOD trial.[89]

BTX has also been evaluated for SOD with recurrent pancreatitis. A study by Wehrmann and colleagues looked at the efficacy of BTX in preventing recurrent pancreatitis owing to SOD in 15 women with recurrent pancreatitis with manometric evidence of SOD.[86] Patients were treated with a single injection of BTX 100 U into the ampulla of Vater, and the effectiveness of treatment was monitored over 3 months. Twelve patients (80%) remained asymptomatic at 3-month follow-up; however, 11 patients developed recurrent symptoms at 8 months and underwent pancreatic or biliopancreatic sphincterotomy with long-term remission at 15 months. Of the 3 patients who did not respond to therapy, 1 showed manometric evidence of elevated pancreatic sphincter pressure and benefited from pancreatic sphincterotomy.[86] However, 3 months for follow-up is a short time frame for making substantial conclusions given that recurrent acute pancreatitis may occur as often as every 2 years. Additionally, manometry findings and symptoms do not always correlate.

In acalculous biliary pain, BTX injections have been used for relaxing the sphincter of Oddi.[90] One study found that in 25 patients with acalculous biliary pain, 44% had a positive response to injection of BTX 100 U into the sphincter of Oddi. All of these patients who underwent sphincterotomy had resolution of pain. Of those who did not respond to BTX, only 80% improved with sphincterotomy. BTX injections into the sphincter of Oddi may help direct therapy for patients with acalculous biliary pain.[90,91]

In a prospective clinical phase 1/2 trial in 2017, preoperative BTX injection into the sphincter of Oddi was used as a novel approach to reduce the incidence of postoperative pancreatic fistula after distal pancreatectomy. None of the 29 patients injected with BTX had clinically relevant fistulas, compared with 33% of the case-control patients (P<.004).[92] A retrospective study attempted to reproduce these results in 19 patients but found no statistical significance.[93] Regardless, the data have prompted a government-sponsored, multicenter, pilot RCT in Germany (PREBOT; registration number: DRKS00020401).[94]

In summary, although existing data are very limited, some studies may suggest proof of principle that BTX could provide short-term benefit and may be predictive of response to sphincterotomy in certain patients with sphincter of Oddi disorders. Most of the literature, however, appears to be of limited value owing to small study sizes, uncontrolled series, unclear gold standard, limited duration of follow-up, and the bulk of the supportive data being for a condition (type III SOD) for which it is now believed that sphincter ablation is of no value. Additional methodologically rigorous research is necessary to understand whether BTX plays any role for this condition.

Chronic Anal Fissures

Anal fissures are tears in the anoderm that start at the anal verge and can extend to the dentate line and typically arise in the mid-posterior position of the anus. They are thought to occur secondary to increased anal sphincter pressure in the setting of ischemia. Symptoms can include painful defecation and rectal bleeding. Most acute fissures heal by themselves within several weeks. If anal fissures last more than 4 to 6 weeks, they are considered to be chronic. For CAFs, therapies are aimed at decreasing sphincter tone to help increase blood flow and promote healing. Treatments can include topical nitroglycerin, oral nifedipine, BTX injections, or lateral internal sphincterotomy (LIS).[95]

Many studies have looked at the effectiveness of BTX injections vs placebo or alternative noninvasive treatments for CAFs (see eTable 2 at www.gastroenterologyandhepatology.net).[96-110] In several studies, BTX injections were more effective than placebo or nitroglycerin ointment and had fewer side effects.[96,97] Whether the injection location impacts the effectiveness of healing has also been studied. One theory is that the internal anal sphincter (IAS) has fibrosis at the site of posterior fissures that may delay healing. Patients who received anterior injections of BTX had lower resting IAS pressures and faster healing compared with patients who received posterior injections (88% vs 60%, respectively; P=.025).[98] Increasing the number of injections (bilateral injections vs a single injection) did not significantly affect outcomes.[99] The optimal dosage for BTX injections remains unsettled for symptom improvement despite multiple small studies.[100] A 2016 meta-analysis analyzed dose-dependent efficiency of BTX (5-150 U) among 1577 patients over 34 prospective studies and found no significant difference in terms of effectiveness, postoperative complications, or healing rates.[101] There was no significant correlation between dose and recurrence of symptoms or between dose and long-term efficacy of treatment.[102,103]

Although the gold standard for CAFs is LIS, BTX can be a safer alternative with lower risk of side effects (eg, anal incontinence, bleeding, pain, abscess, fistula); however, long-term efficacy is lower. LIS is superior in sustained response, but BTX has fewer complications and faster healing times.[104] Meta-analyses in the past 2 decades have included many randomized trials on different treatment options for CAFs; however, the trials have had poor quality of evidence secondary to heterogeneity of the population, risk of bias, and inadequate

clinical follow-up. The strongest quality of evidence was comparing LIS with general medical therapy.[105-107] LIS is superior to nonsurgical therapies in terms of sustained treatment and low recurrence, but has an overall higher rate of anal incontinence (3.4%-4.4% in 1 study and up to 16% in another), which is dependent on the surgeon's skill.[104,105] In comparison, complication rates with BTX were close to zero, with some patients having mild transient incontinence. BTX was also superior to other nonsurgical methods such as nitroglycerin and oral nifedipine. Combination therapy with BTX and nitroglycerin or oral nifedipine had moderate improvement in healing.[108,109] Results were also statistically better with a combination of BTX and oral nifedipine compared with nitroglycerin and PD. In patients with a history of LIS and recurrent anal fissures, BTX can be used therapeutically and diagnostically to identify those who would not be suitable for further surgical LIS if transient fecal incontinence developed.[110]

BTX may be an option in patients who are not optimal candidates for LIS or for those who prefer less-invasive forms of treatment. BTX is a viable treatment modality for elderly patients, those who have a higher risk of fecal incontinence with surgery, those who prefer to avoid surgical management, and those with a history of prior sphincterotomy. When BTX's effect wanes, repeat injections can be offered.[104,107-109] Its short-term response rate is often greater than 60%, symptoms tend to improve with retreatment, and it can be more cost-effective given the unforeseen costs of treating potential complications of surgery.[111] Surgical intervention is best considered in patients with persistence/recurrence, noncompliance, or intolerance to other conservative treatments. Although some reviews suggest that medical management and BTX provide little more than placebo, their evidence is low quality and from smaller studies.[112]

Overall, larger high-quality multicenter studies are needed with standardized selections of patients, doses, and injection techniques to make a more definitive conclusion. In the interim, BTX may be a good first option in CAFs, as it is a cost-effective approach that can provide symptomatic relief and healing while avoiding permanent alterations to the anal sphincter and complications of incontinence or other systemic side effects.

Chronic Idiopathic Anal Pain

Anal pain can be attributed to structural or functional causes, often with an inappropriate loop between spasms and pain contributing to a chronic pain syndrome. Functional causes tend to be difficult to manage conservatively. BTX has been studied in chronic functional anorectal pain. In a study evaluating 113 patients at a tertiary proctology clinic, patients with hypertonia of the anal sphincter received 2 injections of BTX 30 U and patients with hypertonia of the levator ani received 2 injections of 40 U. If hypertonia was present in both areas, patients received both treatments. Of those patients who received both treatments, 47% had complete resolution of pain, 20% had temporary resolution with relapse within 3 months, and 33% had poor or no response to therapy.[113]

Anismus

Anismus (also known as pelvic floor dyssynergia) is the inappropriate contraction of the pelvic floor muscles when attempting to defecate. This involves the puborectalis muscle and external anal sphincter (EAS) and can lead to chronic severe constipation via outlet obstruction.[114-116] It is hypothesized that this inappropriate contraction is a maladaptive learned behavior. However, some research in patients with Parkinson disease suggests that this dysfunction may also present as a form of focal dystonia.[117] As a result, some physicians have used BTX injections to lower puborectalis tone and facilitate defecation. The mainstay of treatment in patients with anismus is typically biofeedback, which leads to improvement in up to 70% of patients. Surgery is not an effective treatment.[111] There is some evidence that BTX use in these patients can be effective, although the quality of data is poor because it mainly comes from small uncontrolled, open-label, single-group trials.

In 1988, the first study evaluated 7 patients with anismus and constipation who received BTX injection of unknown dosage into the EAS. Patient symptom scores showed significant improvement correlating with reduced maximum voluntary anal canal squeeze pressure and improvement in anorectal angle on straining; however, 2 of the 7 patients experienced fecal incontinence.[3] In a small study of 4 patients who were injected at 2 sites in the puborectalis muscle with BTX 30 U, 3 patients (75%) showed improvement by 8 weeks (the other was lost to follow-up). There was significant improvement in anal tone (96.2 mm Hg vs 42.5 mm Hg) at 4 weeks (P=.003) and (63.2 mm Hg vs 22 mm Hg) at 8 weeks (P=.009), as well as significant improvement in anorectal angle (94º vs 114º; P=.01). Two of the patients had sustained response for up to 1 year, whereas 1 patient required repeat injections at 16 weeks and 8 months.[118] In 2006, 15 patients with anismus received onabotulinumtoxinA 25 U into the EAS; improvement was seen in 87% of patients with an average remission time of 4.8 months.[119] Similar results were seen in a prior study evaluating BTX injections into the EAS for nonrelaxing puborectalis syndrome.[120] A 2016 systematic review of 189 patients from 7 trials evaluated the response of anismus to BTX injection. Five

studies used lateral EAS injections, whereas 2 studies used a combination of lateral and posterior injections. A median injection of 100 U resulted in improvement in 77.4% of patients at 1 month (measured via balloon expulsion test, EMG, and defecography). However, that number rapidly dropped to 46% at 4 months, with 7.4% developing complications after injection.[121] Thus, although initial improvement can be seen, there tends to be a rapid deterioration of effect by 4 months; however, it may be possible to combat this with repeat injections. Larger studies are needed.

The combination of BTX and biofeedback training can be effective. A 2014 study looked at 31 patients with anismus who failed simple biofeedback training and evaluated the effects of BTX injection with biofeedback training. The researchers administered BTX 100 U into the puborectalis muscle and EAS consecutively during needle withdrawal and then provided biofeedback training 2 weeks after injection. Twenty-three of the patients had success and reported satisfaction throughout an 8-month period.[122]

In patients with Parkinson disease and outlet-type constipation secondary to focal dystonia of the pelvic floor, BTX injections led to improvement in 55% in terms of symptoms, anorectal manometry, and defecography. However, the study's results were weak in strength owing to its small size (N=18) and lack of a placebo group.[117]

Outlet obstruction can also be caused by anterior rectoceles, which, in some cases, are thought to form secondary to failure of the puborectalis muscle to relax. Initial management usually involves a high-residue diet with a combination of laxatives and enemas as needed. Although there can be success with surgical options (transanal, transperineal, or transvaginal approaches), they come with the risk of impaired anal sphincter function, particularly with the transanal approach. Thus, the use of BTX injections in this patient population has been examined. In 2001, an open-label study of 14 women with anterior rectoceles treated with ultrasound-guided BTX injections found that 64% had symptomatic improvement, and there was a significant reduction in rectocele depth (4.3 cm to 1.8 cm; $P<.05$). At 1 year, no patients required digital assistance to defecate and had evidence of rectocele on digital examination, although 28.5% had defecographic evidence of a rectocele.[123]

Overall, BTX injections are safe and a reasonable option for patients with chronic functional anal pain with a relatively low risk of complications. Early treatment in patients after 3 to 6 months of pain can be a plausible option to prevent behavioral changes such as paradoxical contractions of the pelvic floor (pelvic dyssynergia), which may require further combination of BTX injections and behavioral modification therapies. Additional treatments for recurrent pain can be beneficial; however, larger RCTs are needed for further evaluation.

Postsurgical Hemorrhoidectomy Pain

In patients who undergo hemorrhoidectomy, the resting pressure of the anal canal can often be significantly elevated. Thus, postsurgical hemorrhoidectomy pain is thought to be secondary to spasms of the IAS. The purpose of BTX injection in postsurgical hemorrhoidectomy pain is to relax the IAS, thereby relieving pain. In a double-blind RCT of BTX use in postsurgical hemorrhoidectomy pain, 50 patients were randomized into treatment and placebo groups for injection of BTX (20 U) vs saline. On postoperative days 6 and 7, there was a significant improvement in pain compared with the placebo group ($P<.05$).[124] Similarly, a study of 30 patients with third- and fourth-degree hemorrhoids compared BTX (20 U) with normal saline injections at the time of surgery. On day 5 postsurgical hemorrhoidectomy, maximum resting pressures, time to wound healing, and postoperative pain at rest and with defecation were significantly decreased in the BTX group ($P<.05$). However, maximum resting pressures returned to preoperative levels in both groups at 30 days postoperation.[125] In an RCT, 90 patients were split into control vs BTX (30 U) groups. At 12 and 24 hours postoperatively, there was a significant reduction in visual analog pain score ($P<.001$ and $P=.003$, respectively).[126]

However, an RCT of 32 patients found no significant difference between BTX and placebo in decreasing maximal pressure and squeeze pressure at 5 days postoperation.[127] Complications related to BTX injections involved transient incontinence (0%-33%) and typically involved flatus lasting 3 to 12 weeks. Ultimately, more high-powered studies are needed to determine how helpful BTX is in this setting, although it appears that maximal anal pressures were reduced and overall healing time was shortened by at least a week (average healing time 3-5 weeks) in patients who received BTX.[125,127]

When compared with topical glyceryl trinitrate (GTN), BTX is superior at 7 days for maximal relief of anal pain at rest and for overall analgesic required. Both are equally efficacious at reducing pain scores on defecation, and there was no significant difference in wound healing time. However, topical GTN had more side effects, including increased headaches.[128]

Overall, the use of BTX in postsurgical hemorrhoidectomy pain can be useful for decreasing symptoms up to 1 week after the procedure, including pain at rest and with defecation; however, there is some possibility of transient side effects, including flatus that may persist for up to 3 months. BTX may be a good option in patients with poor compliance to medical therapy postoperatively.

Table 3. Recommendations for BTX Use in the Gastrointestinal Tract

	Disorder	Recommendations	Quality of Evidence (GRADE)[a]
Esophagus	Cricopharyngeal dysphagia	BTX can be considered an alternative to surgical myotomy in patients who are not optimal surgical candidates or who seek only temporary relief of symptoms. It can also be used as a potential diagnostic test to predict response to surgical myotomy	Moderate
	Achalasia	BTX should be considered for type 1 and 2 achalasia in elderly patients and those at high risk for surgical complications, patients seeking short-term relief, patients avoiding more aggressive therapy, or patients who are not candidates for pneumatic dilation or myotomy owing to comorbidities. BTX is not recommended for type 3 achalasia	High
	EGJOO	BTX can be considered a conservative approach in patients with associated dysphagia or chest pain, although treatment durability may be limited	Very low
	Spastic esophageal disorders	In patients with dysphagia as the primary symptom with lack of response to dilation or smooth muscle relaxation, esophageal BTX injection 2 cm and 7 cm above the lower esophageal sphincter should be considered	Low
Stomach	Gastroparesis	BTX is not currently recommended for the treatment of gastroparesis	Moderate
	Obesity	BTX is not currently recommended for the treatment of obesity. Although fundal injections have shown some benefit, more large-scale trials are needed	Moderate
Duodenum	Sphincter of Oddi disorders	BTX injections may be considered for patients at high risk for sphincterotomy. They can provide transient relief with few side effects, may be predictive of patients who would benefit from sphincterotomy, and may possibly reduce the rates of recurrent pancreatitis	Very low
Anus/ Pelvic Floor	Chronic anal fissure	BTX is a viable treatment for elderly patients, those who have higher risk of fecal incontinence with surgery, those who prefer to avoid surgical management, and those with a history of prior sphincterotomy	High
	Chronic idiopathic anal pain	It is reasonable to consider BTX injections as an option either as solo therapy or in combination with CBT, although CBT remains the gold standard	Very low
	Anismus	BTX injection into the external anal sphincter or puborectalis muscle may be considered as a safe option, although durability may be limited	Very low
	Postsurgical hemorrhoidectomy pain	BTX injection can be reasonable to reduce postsurgical hemorrhoidectomy pain, improve overall healing time, and reduce resting anal pressures. Its side-effect profile is lower than that of other pharmacotherapies	Moderate

[a]Quality of evidence based on the GRADE system.[129]

BTX, botulinum toxin A; CBT, cognitive behavioral therapy; EGJOO, esophagogastric junction outflow obstruction; GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

Conclusion

For 30 years, BTX has been studied as a treatment modality in a variety of GI disorders with varying results. The appeal of BTX comes from its simplicity of administration, good safety profile, reliability in decreasing muscular tone, and effective response rate in patients who have failed conventional therapies. However, there are several drawbacks that limit its use, including the lack of long-term efficacy in many GI disorders, which leads to repeat administrations, additional costs associated with multiple procedures, and unclear effect in certain disorders such as gastroparesis and obesity. Overall, BTX has well-established efficacy in achalasia, CAFs, and cricopharyngeal dysphagia. In disorders such as achalasia, it can serve as a reliable option for patients at higher risk

of adverse events from myotomy (eg, patients who are elderly or have multiple comorbidities) and can be palliative in nature. Additionally, BTX can be an option for patients who favor a more conservative approach when there is fear of potential adverse events from surgery (eg, fecal incontinence after LIS).

However, data in other areas of the GI tract are limited by the number of low-powered trials, heterogeneity of patients, studies without placebo groups, and lack of blinding in open-label trials. There is a strong need for further investigation of BTX use in larger RCTs in various areas of the GI tract. Also, many studies are difficult to compare owing to differing administrative techniques, injection sites, and dosages, as well as variable small patient populations in areas such as anismus, gastroparesis, and obesity. Establishing larger well-designed randomized trials with less heterogeneity among patients and intervention techniques may allow for stronger support for or against BTX use in these disorders.

In future studies, methods that could potentially prolong the duration of action of BTX injections or combine them with therapies that could target additional neuronal pathways in the GI tract would be worth investigating. Methodologically rigorous prospective studies are needed to define the exact role of BTX for some indications. Table 3 summarizes the current indications for BTX use in the GI tract in the opinion of the authors, as assessed by the quality of evidence.[129]

Disclosures

The authors have no relevant conflicts of interest to disclose.

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eTable 1. BTX Use for Achalasia

Study	Study Design	Type of Intervention	Sample Size	Results
Pasricha et al[34]	Double-blinded RCT	BTX vs placebo	21	67% improved at 6 weeks
Annese et al[37]	RCT	BTX vs placebo vs PBD	16	100% improved at 1 month, but 88% needed repeat injections. BTX was comparable with PD
Annese et al[42]	Clinical trial	BTX	57	88% of patients had improvement in symptoms and LES pressure (P<.001) at 1 month. 75% were still in remission at 2 years, although with repeat injections
Annese et al[29]	RCT	Ona-A vs abo-A	78	Similar efficacy up to 6 months
Horgan et al[40]	Prospective cohort study	BTX + HM vs HM	57	Injection of BTX significantly increased the technical difficulties of HM and thus potential risk of esophagomyotomy
Vaezi et al[35]	RCT	BTX vs PD	22 in BTX group 20 in PD group	At 1 year, PD was more effective than BTX (70% v 32%; P=.02)
Annese et al[30]	RCT	BTX dose comparison	118	82% of patients were responders at 1 month. No dose-related effect was observed
Wehrmann et al[32]	Pilot clinical trial	Manometrically guided endoscopic BTX injection	7	Symptoms decreased by 50% at 6 weeks (P=.02). At 1.5 years, the mean symptom score for all patients was significantly lower than before treatment (P=.03)
Brant et al[33]	RCT	BTX in Chagas disease	24	Clinical improvement of dysphagia was significant in BTX group vs placebo at 6 months (P<.001). Esophageal emptying time was lower in BTX group vs placebo (P=.04) after 90 months
Zaninotto et al[39]	RCT	BTX vs HM	80	Similar results between groups at 6 months, but higher rate of relapse in BTX group at 2 years (P<.05). At 2 years, 87.5% of surgical group was symptom-free vs 34% of BTX group (P<.05)
Kroupa et al[41]	Comparative prospective study	BTX + PBD vs PBD	91	Effect of therapy lasted in 75%. The 5-year remission rate in the combined group was higher but not significant (P=.07)
Leyden et al[38]	Systematic review	BTX vs PD	7 RCTs involving 178 patients	PD was more effective than BTX after 6 months
Marjoux et al[36]	Retrospective study	BTX in achalasia and other hyperplastic esophageal disorders	45	No clear difference in response was observed according to manometric diagnosis. 71% were significantly improved after 2 months, and 57% remained satisfied for more than 6 months. There was no response to endoscopic BTX injection in type 3 achalasia

Abo-A, abobotulinumtoxinA; BTX, botulinum toxin A; HM, Heller myotomy; LES, lower esophageal sphincter; ona-A, onabotulinumtoxinA; PBD, pneumatic balloon dilation; PD, pneumatic dilation; RCT, randomized controlled trial.

eTable 2. BTX Use for CAFs

Study	Study Design	Intervention	Dose(s)	Sample Size	Results
Maria et al[96]	RCT	BTX vs saline injection	BTX 20 U vs saline	30	73% had resolution of their fissures at 2 months compared with 13% in the placebo group
Brisinda et al[97]	Therapeutic RCT	BTX vs topical nitroglycerin	BTX 20 U vs 0.2% topical nitroglycerin twice daily	50	96% of patients in the BTX group had fissure healing vs 60% in the nitroglycerin group (P=.005)
Maria et al[98]	RCT	BTX posterior midline vs anterior midline of IAS	BTX 20 U	50	Anterior injection resulted in lower resting anal pressure and earlier scar healing
Brisinda et al[100]	Clinical trial	Low-dose vs high-dose BTX injection	Low-dose group: BTX 20 U (if recurrence, then 30 U) High-dose group: 30 U (if recurrence, 50 U given)	50	High-dose group was more effective at 1 month (87% vs 73%; P=.04) but had similar efficacy at 2 months. Resting anal pressure and voluntary pressure were similar between groups
Menteş et al[104]	RCT	BTX vs LIS	BTX 20-30 U	61 in BTX group 50 in LIS group	BTX group had earlier recovery and fewer complications compared with sphincterotomy, although repeat injections may be required to maintain response. Both groups had similar healing rates at 6 months, but LIS was more effective at 1 year
Tranqui et al[109]	Retrospective comparative study	Nitroglycerin + PD vs nifedipine + BTX	Nitroglycerin + PD vs topical nifedipine + BTX 30-100 U	88	The combination of nifedipine and BTX was superior to nitroglycerin and PD with respect to both healing and recurrence rate (P<.05)
Sajid et al[106]	Meta-analysis of RCTs	LIS vs BTX	NA	279	BTX and LIS are comparable treatments for CAFs. LIS had higher complication rates and transient incontinence rates but had a higher healing rate and a lower recurrence rate than BTX
Brisinda et al[110]	Therapeutic clinical trial	BTX for recurrent anal fissure following LIS	BTX 30 U or abo-A 90 U	80	BTX was efficacious in patients with recurrent anal fissure following LIS
Chen et al[105]	Meta-analysis of RCTs	BTX vs LIS	NA	489 patients over 7 trials	LIS was superior to BTX in terms of healing rate and recurrence rate. BTX was safer and associated with a lower rate of incontinence
Asim et al[108]	Prospective RCT	BTX vs BTX + GTN	Group A: 20 U Group B: 20 U + topical 0.2% GTN	41	Fissure healing was similar in the 2 groups at 6 and 12 weeks. GTN group had more headaches (58%)
Bobkiewicz et al[101]	Meta-analysis	Analysis of dose-dependent efficiency of BTX	BTX 5-150 U	1577	There is no dose-dependent difference in efficiency, postoperative incontinence, or healing rate (P=.07)
Dat et al[102]	Retrospective study	Effectiveness of varying doses of BTX in overall healing	BTX 20-50 U (average 33 U)	101	No significant correlation between dose and recurrence of symptoms. Pain at the first postoperative visit was a strong indicator for recurrence (P=.003)
Ravindran et al[103]	Retrospective case-control study	High-dose vs low-dose BTX	High-dose (BTX 80-100 U) vs low-dose (BTX 20-40 U)	158	Patient satisfaction was higher in the high-dose group (90% vs 78%; P=.05) and long-term recurrence (6 months) was lower (23% vs 53%; P=.0001)
Nelson et al[107]	Meta-analysis of RCTs	Nonsurgical treatment options vs surgical treatment options	14 different operations and 29 nonsurgical options	148	LIS was superior to nonsurgical therapies in achieving sustained cure of fissures but with higher incontinence risk
Pilkington et al[99]	Randomized single-center trial	Single BTX injection vs bilateral BTX injection	Single (100 U) Bilateral (50 U + 50 U)	100	Unilateral injection was similar to bilateral injection in healing and improving fissure pain without worsening of continence

Abo-A, abobotulinumtoxinA; BTX, botulinum toxin A; CAF, chronic anal fissure; GTN, glyceryl trinitrate; IAS, internal anal sphincter; LIS, lateral internal sphincterotomy; NA, not available; PD, pneumatic dilation; RCT, randomized controlled trial; U, units.