



# Botulinum Toxin for Gastrointestinal Disorders: Therapy and Mechanisms

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**Botulinum toxin has gained widespread acceptance as a treatment option for various spastic gastrointestinal disorders such as achalasia, gastroparesis, sphincter of Oddi dysfunction, chronic anal fissures, and pelvic floor dyssnergia, despite the lack of strong evidence supporting its use in many of these disorders. This review summarizes the trials investigating the use of BoNT since it was first utilized as a treatment in achalasia. BoNT has proven to be safe, but long-term efficacy in many disorders has not been observed, primarily due to its relatively short duration of action. BoNT may be most useful in confirming a diagnosis which can lead to a more definitive treatment modality. Furthermore, its safety profile allows it to be a useful alternative in patients who are at high risk for invasive procedures.**

*Keywords:* Botulinum toxin; Achalasia; Anal fissure; GI spastic disorders

## INTRODUCTION

Although the therapeutic potential of botulinum toxin for skeletal muscle disorders was first realized in the 1970s, it was not until nearly two decades later that it was also shown to be effective in the gastrointestinal tract (Pasricha *et al.*, 1993; 1994b; 1995; 1996). Since then, however, there has been a rapid increase in the number of reports in a variety of GI conditions characterized by dysfunctional smooth muscle. This article will review the efficacy of this toxin in the treatment of these conditions.

## BACKGROUND

Normal motility of the gastrointestinal tract depends on intrinsic neurons contained in the enteric nervous

system (ENS), with significant modulatory input being provided by the central nervous system (CNS) via autonomic sympathetic and parasympathetic nerves. Immediate control of muscle tone in the gut reflects a balance between both excitatory (predominantly cholinergic) and inhibitory (predominantly nitrinergic) innervation (Hansen, 2003). In some disease states, this balance is disrupted, usually due to a relatively selective loss of inhibitory neurons. In this setting, BoNT, by blocking excitatory neurotransmitter release, can restore the balance and cause a decrease in the resting tone of the muscle involved.

Although BoNT can clearly inhibit the release of acetylcholine, little else is known about its effects in gastrointestinal muscle. Thus, while nitric oxide release is not affected (which is to be expected, since this is not a vesicular process) (Olgart *et al.*, 2000), the specific effects on other potentially important neurotransmitters such as vasoactive intestinal peptide (VIP) or substance P has not been well documented. Further, there is some suggestion that it may also inhibit the responsiveness of smooth muscle to exogenous stimuli, an effect that is quite unique to the GI tract (James *et al.*, 2003).

## SPECIFIC DISORDERS

### Achalasia and Other Esophageal Disorders

The major pathophysiological lesion in achalasia, which means failure to relax, results from a relatively specific loss of nitrergic inhibitory neurons of the lower esophageal sphincter (LES), resulting in an inability of the sphincter to relax after swallowing. This results in a functional obstruction and dysphagia (Csendes *et al.*, 1985). Although no cure exists for achalasia, there are a number of palliative treatments available including surgical myotomy, pneumatic dilation, and BoNT injections into the LES. Surgical myotomy has proven

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durable, but is associated with increased morbidity and mortality in high-risk surgical patients. Pneumatic dilation of the sphincter results in an initial symptomatic improvement in 60-90% of patients but repeated dilations are often necessary. Furthermore, the procedure carries a small but significant risk of esophageal perforation (Reynolds and Parkman, 1989). Thus, BoNT provides a potentially attractive alternative to the above treatment methods.

### **Technique**

Endoscopic injection of 25 units (U) of BoNT in 4 quadrants of the LES is generally the standard of care.

### **Review of trials**

The efficacy of BoNT in achalasia has been proven by the results of several randomized trials comparing it to either placebo or pneumatic dilation. Table I summarizes the response rates to BoNT in patients with achalasia. In general, 75%-100% of patients show an initial response but more sustained improvement (beyond 6 months) is seen in about two-thirds. For unclear reasons, it appears that patients older than 50 years of age respond at a higher rate (82% vs 43% in younger patients). Similarly, patients with so-called vigorous achalasia (with the esophagus retaining some contractile ability) respond at a higher rate (100% vs 52% with classic achalasia) (Neubrand *et al.*, 2002).

### **Comparisons to Other Treatment Modalities**

Several studies have compared BoNT to pneumatic dilation with most reporting similar initial clinical or manometric responses (Table I). However, the 1-year remission rate after a single injection is markedly inferior for BoNT, which is to be expected given its pharmacological properties. In the only study comparing the two modalities in a head to head comparison, 80 patients were randomized to receive 100 U of BoNT or laparoscopic surgical myotomy with fundoplication. After 6 months, symptom scores improved more in surgical patients (82% confidence interval [CI] 76-89 vs 66% CI 57-75,  $P < 0.05$ ). The drop in lower esophageal sphincter pressure was similar in the 2 groups; the reduction in esophageal diameter was greater after surgery (19% CI 13-26 vs 5% CI 2-11,  $P < 0.05$ ). The only complication in the surgical group was one patient bled at the trocar site. The probability of being symptom-free at 2 years was 87.5% after surgery and 34% after BoNT ( $P < 0.05$ ) (Zaninotto *et al.*, 2004a). The same group investigated the cost effectiveness of the two modalities and concluded that BoNT was more cost effective in the short term, but at 2 years, cost between the two groups was similar (Zaninotto *et al.*, 2004b,c).

### **Adverse Effects**

BoNT injections into the GI tract appear to be quite safe with very few, if any, reports of serious adverse effects. The incidence of gastroesophageal reflux has not been well characterized in most studies but has been reported to be about 20%, by symptoms, at least. There has also been some question in recent years whether BoNT prior to dilation or myotomy complicates the more invasive procedures, possible secondary to fibrosis of the LES. However, although previous injection of botulinum toxin (or pneumatic dilation for that matter) may make myotomy more challenging technically because of obliteration of tissue planes, this does not appear to affect the final outcome after myotomy (Bonavina *et al.*, 1999; 2000; Horgan *et al.*, 1999).

### **Other Esophageal Disorders**

Botulinum toxin has also been used in a variety of less well characterized esophageal conditions including diffuse esophageal spasm (DES) and patients with non-cardiac chest pain, suspected to be on the basis of a dysfunctional esophagus. DES is a condition that is related to achalasia and may be associated with LES dysfunction as well. The largest clinical trial assessing the effect of BoNT in patients with diffuse esophageal spasm evaluated 9 patients (Storr *et al.*, 2001). Each patient was given 100 U of BoNT diluted in 10 ml of saline solution and injected endoscopically at multiple sites along the esophageal wall beginning in the region of the lower esophageal sphincter and moving proximally in 1 to 1.5-cm intervals, and into endoscopically visible contraction rings. At week 4, 8 patients had a significant reduction in symptom score, and 4 patients required subsequent injections over a 2-year period (Storr *et al.*, 2001). Other than this study, there have only been a few case reports using this technique (Henry and Prado, 1998; Storr *et al.*, 2005). Unfortunately, there have been no other clinical trials evaluating BoNT as a treatment option for this disorder.

In addition to dysphagia and regurgitation, chest pain can be associated with achalasia, DES, ineffective esophageal motility (IEM), and isolated LES dysfunction, which may respond to BoNT administration as shown in previous studies (Pasricha *et al.*, 1995; Annese *et al.*, 1996). A study, with improvement of chest pain as the primary end-point, evaluated 29 patients with non cardiac chest pain who received 100 U of BoNT injection into the LES - same as the treatment regimen for achalasia. Seventy-two percent of the patients responded with at least 50% reduction in chest pain (Miller *et al.*, 2002a).

Table I

Year Published	No. of patients	BoNT Dose	Comparative Treatment Group	Follow-up	Results
Pasricha <i>et al.</i> , 1995	21	80 U	Saline	6 mo.	67% remission rate at 6 mo. No placebo effect
Annese <i>et al.</i> , 1996	16	100 U	Saline, pneumatic dilatation	1 yr	53% response rate at 6 mo. Comparable to pneumatic dilation at 1 yr
Vaezi <i>et al.</i> , 1999	42	100 U	Pneumatic dilation	1 yr	70% remission rate with pneumatic dilation at 1 yr 32% remission rate with BoNT at 1 yr
Muehldorfer <i>et al.</i> , 1999	24	100 U	Pneumatic dilation	30 mo.	0% remission rate in BoNT group at 30 mo. 60% remission rate in dilation group at 30 mo.
Annese <i>et al.</i> , 1999	78	100 U Botox	250 U Dysport	6 mo.	Approximately 70% remission rate at 6 mo. in both groups
Annese <i>et al.</i> , 2000	118	100 U X 2	50 U, 200 U	7-24 mo. Mean, 12 mo.	19% relapse rate in 100 U X 2 group >40% relapse rate in other groups Vigorous achalasia was a predictor of response
Mikaeli <i>et al.</i> , 2001	40	100 U	Pneumatic dilation	12 mo.	53% remission rate with dilation 15% remission rate with BoNT 100% remission rate with 2nd dilation 60% remission rate with 2nd BoNT injection
Bansal <i>et al.</i> , 2003	34	80 U	Witzel dilation	Mean, 4 mo.	89% remission rate with dilation 38% remission rate with BoNT
Zaninotto <i>et al.</i> , 2004	37	100 U X 2	Laparoscopic myotomy	2 yr	90% remission rate with surgery 34% remission rate with BoNT No difference in cost effectiveness at 2 yr
Zaninotto <i>et al.</i> , 2004	80	100 U X 2	Laparoscopic myotomy	6 mo.	82% remission rate with surgery 66% remission rate with BoNT

### Summary

BoNT administration for achalasia has proven to be safe and effective at least for short-term relief of symptoms (less than 6 months). Patient factors, such as risk of surgery, age, and life expectancy, should be considered prior to choosing a treatment modality for achalasia. If patients are at high risk for surgery, BoNT is a reasonable option. If the patient is low risk for surgery, surgical myotomy and fundoplication provide the most durable treatment option.

### Cricopharyngeal Dysphagia

The cricopharyngeus muscle comprises a major component of the upper esophageal sphincter (UES). Cricopharyngeal dysphagia, either idiopathic or secondary to various neurologic or muscular conditions (Kelly, 2000), is characterized by incomplete or poorly coordinated opening of the UES during the pharyngeal

phase of swallowing. This proximal dysphagia can result in laryngeal penetration or tracheal aspiration of swallowed food. Traditionally, cricopharyngeal myotomy (CPM) has been the mainstay of treatment but other options such as dilation and BoNT injection have been used with good results (Ravich, 2001).

A number of injection techniques have been employed including rigid endoscopy with electromyographic control, flexible endoscopy, and an open technique with various doses (10-50 U) (Brant *et al.*, 1999; Bachmann *et al.*, 2001; Haapaniemi *et al.*, 2001; Shaw and Searl, 2001; Moerman *et al.*, 2002; Parameswaran and Soliman, 2002; Restivo *et al.*, 2002; Yokoyama *et al.*, 2003). Endoscopically, 3 to 4 injections of BoNT can be delivered to the dorsomedial and bilateral ventromedial compartments of the cricopharyngeus muscle (Shaw and Searl, 2001). Furthermore, the location of the cricopharyngeus muscle has been verified

Table II

Year Published	No. of patients	BoNT Dose	Comparative Treatment Group	Follow-up	Results
Maria <i>et al.</i> , 1998	30	20 U	Saline	2 mo.	73% healing rate with BoNT 13% healing rate with saline
Brisinda <i>et al.</i> , 1999	50	20 U	0.2% nitroglycerin ointment	2 mo.	96% healing rate with BoNT 60% healing rate with NTG
Maria <i>et al.</i> , 2000	50	20 U	Posterior vs anterior application	2 mo.	60% healing with posterior 88% with anterior
Lysy <i>et al.</i> , 2001	30	20 U	BoNT vs BoNT + topical isosorbide dinitrate	12 wk	Higher healing rates at 6 wk in combo treatment Similar healing rates at 12 wk
Brisinda <i>et al.</i> , 2002	150	20U + 30 U, 2 <sup>nd</sup> dose if fissure persists	30U + 50 U, 2 <sup>nd</sup> dose if fissure persists	2 mo.	Increased healing rates at higher dose, increased rates of incontinence at higher doses
Mentes <i>et al.</i> , 2003	111	30 U	lateral internal sphincterotomy	12 mo.	94% healing rate with surgery 8 cases of anal incontinence 75.4% healing rate with BoNT
Siproudhis <i>et al.</i> , 2003)	44	100 U Dysport	Placebo	4 wk	No difference in healing rates
Brisinda <i>et al.</i> , 2004	100	50 U Botox	150 U Dysport	2 mo.	No difference in healing rates
Arroyo <i>et al.</i> , 2005	80	25 U	lateral internal sphincterotomy	3 yr	92.5% healing rate with surgery 45% healing rate with BoNT
Iswariah <i>et al.</i> , 2005	38	40 U	lateral internal sphincterotomy	26 wk	91% healing rate with surgery 41% healing rate with BoNT Higher pain scores in BoNT group
Massoud <i>et al.</i> , 2005	50	20 U	lateral internal sphincterotomy	6 mo.	100% healing rate with surgery 88% healing rate with BoNT

by EMG in a number of studies especially in the otolaryngology literature.

### Review of Trials

The use of BoNT to treat UES dysfunction was first described in the mid 1990s with the use of Dysport (80 to 120 U) in 7 patients (Schneider *et al.*, 1994). All patients experienced relief of symptoms. A recent trial evaluated 13 patients with UES dysfunction and evidence of aspiration, receiving 100 U of BoNT. Twelve of the patients demonstrated increased safety and decreased aspiration on oral diet. Furthermore, these 12 patient increased their oral intake and 9 patients no longer required percutaneous endoscopic gastrostomy feeding (Murry *et al.*, 2005). A larger study of 21 patients revealed a clinical response in 43% of patients; with 8 or 11 (73%) of non-responders having a clinical response to surgical myotomy (Zaninotto *et al.*, 2004b). Furthermore, BoNT administration has been shown to be efficacious in

2 patients with inclusion body myositis as the etiology of oropharyngeal dysphagia (Liu *et al.*, 2004). A recent case report was published along with a review of 28 patients with cricopharyngeus muscle spasm. They concluded that patients who obtained better post-treatment results would enjoy longer effective duration. However, advanced age and lower doses of BoNT were negative prognostic factors (Chiu *et al.*, 2004). Mean duration of effect was approximately 7 months and correlated with the presence of cricopharyngeal spasm. The overall response rate from an analysis of the studies ranges from 70% to 100%. Globus sensation, which may be secondary to upper esophageal sphincter dysfunction, may be alleviated with injection of BoNT, as demonstrated in one case report (Halum *et al.*, 2005).

### Summary

Response to BoNT injection may select out a group of patients with higher likelihood of a more durable

response to surgical myotomy (Alberty *et al.*, 2000). Furthermore, non-response may indicate another etiology of dysphagia, *i.e.*, stricture.

### **Gastroparesis**

Gastroparesis or delayed gastric emptying resulting in nausea, vomiting, dyspepsia, and abdominal bloating is a common problem in patients seen by primary care physicians and gastroenterologists. Gastroparesis can occur as a result of poorly controlled diabetes mellitus, post-surgical manifestations, or idiopathic causes. It has been hypothesized that one of the clinical manifestations of gastroparesis is pylorospasm, partially from impaired relaxation and unopposed cholinergic stimulation. Thus, decreasing pylorospasm may increase gastric emptying. In recent years, injection of BoNT into the pylorus has been investigated as a treatment option in this otherwise debilitating disorder.

### **Review of Trials**

The initial study evaluating the efficacy of BoNT in patients with diabetic gastroparesis assessed six patients with abnormal solid phase gastric emptying. Each patient received 100 U of BoNT into the pyloric sphincter, and symptom scores and gastric emptying were assessed after 6 weeks. There was an improvement of subjective symptom scores of 55% (range, 14% to 80%), which was maintained at 6 weeks. In addition, there was a 52% improvement in gastric emptying at 6 weeks (Ezzeddine *et al.*, 2002). Another study investigated the use of BoNT in cases of idiopathic gastroparesis. Ten patients were given 80-100 U of BoNT and a 38% reduction in symptom scores were seen at 4 weeks, which correlated with findings of increased gastric emptying (Miller *et al.*, 2002b). A few case reports have supported the use of BoNT for gastroparesis (Gupta and Rao, 2002; Lacy *et al.*, 2002). A recent study evaluated the effects of BoNT on diabetic gastroparesis for 12 weeks. Eight patients received 200 U of BoNT into the pyloric sphincter, and seven patients completed the 12-week follow-up. Mean symptom scores declined from 27 to 12.1 ( $P < 0.01$ ). Furthermore, six of the seven patients gained weight ( $P = 0.05$ ) and gastric emptying scan time improved in four patients (Lacy *et al.*, 2004). The largest study to address this issue retrospectively evaluated 63 patients who met the study criteria. Gastroparesis was secondary to diabetes in 26 patients (41.2%), after surgery in two (3.2%), and idiopathic in 35 (55.6%). Twenty-seven of 63 (43%) patients experienced a symptomatic response to treatment (100 to 200 U) with a mean duration of 5 months.

Male gender was associated with response to therapy. However, vomiting as a major symptom was predictive of no response to BoNT (Bromer *et al.*, 2005).

### **Summary**

There are as yet no controlled trials on which to confidently base a statement regarding the efficacy of BoNT in this condition. However, based on the studies above, it is clear that the response may be restricted to a subgroup of patients only. Future studies will hopefully address these issues and better define potentially responsive patients by either clinical or physiological criteria.

### **Sphincter of Oddi Dysfunction**

The sphincter of Oddi is a small ring of muscle that surrounds the biliary and pancreatic ducts just before they open into the duodenum. Sphincter of Oddi dysfunction (SOD) is a poorly understood and controversial condition postulated to result in biliary pain, typically in the setting of a previous cholecystectomy. It has also been hypothesized that pancreatic SOD can result in pancreatic type pain and/or recurrent pancreatitis (Geenen *et al.*, 1989). The standard of treatment for SOD currently is endoscopic sphincterotomy, which is a relatively high-risk procedure that is not uniformly effective. Hence there is interest in the use of a simpler procedure such as BoNT to serve as a therapeutic trial - patients who respond to this treatment could then go on for more permanent relief using a sphincterotomy. This was first suggested in a short report on two patients (Pasricha *et al.*, 1994a). Subsequently a larger study was reported, evaluating twenty-two patients who had undergone cholecystectomy and had manometrically confirmed type III SOD (Wehrmann *et al.*, 1998). Six weeks after 100 U of BoNT injected into the sphincter, 12 patients (55%) were symptom-free, but 10 patients (45%) were not. Of the 10 patients who did not experience symptomatic benefit from BoNT injection, 5 had normal basal sphincter of Oddi pressures ( $< 40$  mmHg), and biliary sphincterotomy did not relieve the symptoms of these patients. Two of the remaining 5 patients with sustained sphincter hypertension after BoNT injection benefited from biliary sphincterotomy. Of the 12 patients who initially responded to BoNT injection, 11 patients remained symptom free for a median duration of 6 months. These patients had recurrence of biliary hypertension and responded to biliary sphincterotomy. The authors concluded that response to BoNT injection may select a subset of patients who will respond to biliary sphincterotomy (Wehrmann *et al.*, 1998).

BoNT has also been used with similar intent, although

in an uncontrolled manner in patients with acute recurrent pancreatitis suspected to be due to pancreatic SOD (Muehldorfer *et al.*, 1997; 1999; Wehrmann *et al.*, 1999; 2000).

### Summary

The future role of BoNT injection in the sphincter of Oddi still needs further investigation but current literature supports its use as a therapeutic trial in patients with SOD.

### Anal Fissure

Anal fissures are tears in the anoderm that start at the anal verge and can extend to the dentate line. They can manifest into painful defecation and rectal bleeding. These fissures, which most commonly arise in the mid-posterior position of the anus, are thought to occur secondary to ischemia as a result of increased anal sphincter pressures and decreased blood flow (Schouten *et al.*, 1996). Once chronic fissures develop, treatment options are aimed at interrupting this cycle by reducing sphincter tone, using topical nitroglycerin (Brisinda *et al.*, 1999; Kennedy *et al.*, 1999), BoNT injection, oral nifedipine (Cook *et al.*, 1999; Brisinda and Maria, 2000), or lateral internal sphincterotomy performed surgically (Hananel and Gordon, 1997; Lewis *et al.*, 1988).

### Review of Trials

There are many reports on the efficacy of BoNT for this condition (Table I). These studies include several controlled trials comparing the toxin to either placebo or other modalities. Clinical benefit is seen in the vast majority of patients, typically accompanied by reduction in resting anal sphincter pressure.

The exact site and dose of injection remains somewhat unsettled. Most of the trials to this point have evaluated BoNT administration at the point of the fissure, primarily, the posterior midline area of the anal verge. However, there is evidence that fibrosis of the internal anal sphincter exists at the base of the fissure and is more prominent in this zone than other sites in the smooth muscle (Brown *et al.*, 1989). This fibrosis may decrease the effects of BoNT on sphincter relaxation, thus delaying fissure healing. A study to evaluate this theory was conducted on 50 patients with posterior anal fissures who were either given 20 U of BoNT lateral to the posterior fissure or 20 U of BoNT on each side of the anterior midline. After 2 months, a healing scar was observed in 15 patients (60%) of the posterior midline group and in 22 patients (88%) of the anterior midline group ( $P = 0.025$ ). Resting anal pressure was significantly different from the baseline values at 1 and 2 months in both groups, but the values were signifi-

cantly lower in patients of the anterior midline group (Maria *et al.*, 2000).

Another study evaluated 150 patients with posterior anal fissures, who were treated with BoNT injected in the internal anal sphincter on each side of the anterior midline. Patients were randomized to receive either 20 U of BoNT and, if the fissure persisted, were retreated with 30 U, or 30 U and retreated with 50 U, if the fissure persisted. One month after the injection, examinations revealed complete healing in 55 patients (73%) in the group receiving the lower dose and in 65 patients (87%) in the group receiving the higher dose ( $P = 0.04$ ). Five patients from the second group reported a mild incontinence of flatus that lasted 2 weeks after the treatment and disappeared spontaneously. The values of the resting anal pressure ( $P = 0.3$ ) and the maximum voluntary pressure ( $P = 0.2$ ) did not differ between the 2 groups. However, after 2 months, healing rates were similar between the two groups (89% and 96%). The authors concluded that the higher dose was more effective (Brisinda *et al.*, 2002) but the improved effectiveness was not seen at 2 months.

The gold standard for treatment for anal fissures is surgery, primarily lateral sphincterotomy. However, surgical intervention is associated with a low complication rate resulting in fecal incontinence, hematoma, and wound infection (Argov and Levandovsky, 2000). A recent study compared BoNT injection (20 U to 30 U) and lateral internal anal sphincterotomy. Overall healing rates were similar in both groups at 6 months with 10 of 61 patients requiring a second BoNT injection at 2 months. However, the response rate was higher at 1 and 2 months in the sphincterotomy group; 82% (41/50) at day 28 and 98% (49/50) at the second month ( $P = 0.023$  and  $P < 0.0001$ , respectively, *vs* the BoNT group). The response to BoNT was not as durable as surgery at 12 months, falling to a success rate 75.4% (46/61) with 7 recurrences in the BoNT group, whereas it remained stable in the sphincterotomy group (94%,  $P = 0.008$ ). Sphincterotomy was associated with a significantly higher complication rate, 8 cases of anal incontinence *vs* none in the BoNT group;  $P < 0.001$ . Thus, it appears that surgery is still the more durable treatment option, but associated with more complications (Mentes *et al.*, 2003). These results have been supported in a more recent study (Massoud *et al.*, 2005). However, no difference in healing rates between surgery and BoNT treatment was noted at 14 month follow-up in one study of 21 patients, but this was complicated by a lower healing rate seen in the surgery group compared to other studies (Giral *et al.*, 2004). Some investigators have recommended surgery in younger patients and those with high resting anal pressures, as this is a

risk factor for recurrence (Arroyo *et al.*, 2005b). In one study, healing did not appear to be dependent on a reduction in maximum anal resting pressure, but patients with initial lower resting pressures responded better to BoNT (Thornton *et al.*, 2005). Older patients may benefit from BoNT injection as they may be at higher risk of fecal incontinence after surgery (Arroyo *et al.*, 2005a).

Combination therapy such as nitroglycerine and BoNT has also been evaluated - it appears that this only results in a modest increase in the rate of healing (Watanabe *et al.*, 1975; Brisinda *et al.*, 1999; Vogel, 1999; Madalinski *et al.*, 2001; 2002).

### **Summary**

BoNT injection is efficacious in the treatment of chronic anal fissures. With greater than 60% response rates noted at 2 months with further response to re-treatment, BoNT can be considered a viable treatment option when more conservative treatment fails. In elderly patients, in who rates of fecal incontinence after surgery may be increased, BoNT can be considered first-line treatment. Surgery is still the most durable treatment option, but the risks of fecal incontinence must be weighed carefully against the benefits of the procedure.

### **Pelvic Floor Dyssnergia**

Pelvic floor dyssnergia, also known as anismus, is a common cause of chronic constipation, hallmarked by inappropriate (paradoxical) contraction or a failed relaxation of the puborectal muscle and of the external anal sphincter during defecation. In normal patients, the puborectalis muscle and the external anal sphincter relax to straighten the anorectal angle and open the anal canal. Usually, this alteration in defecation is from maladaptive learning and responds to biofeedback in 60-70% of patients as demonstrated in mostly single group, uncontrolled trials (Bassotti *et al.*, 2004). Surgery has not been shown to be effective and has been largely discouraged as a treatment option (Barnes *et al.*, 1985). There are a limited number of studies evaluating the use of BoNT in pelvic floor dyssnergia.

### **Review of Clinical Trials**

An initial trial evaluating seven patients with constipation and anismus received BoNT of unknown dose into the external anal sphincter. Symptom scores improved significantly correlating with a reduction in the maximum voluntary and anal canal squeeze pressure and a significant increase in the anorectal angle on straining, with subsequent fecal incontinence in two patients (Hallan *et al.*, 1988). In another study with a sample size of four patients with anismus, the dose of BoNT

ranged from 6 U to 15 U injected into the external anal sphincter or puborectalis muscle under electromyography guidance. All four patients, who had numerous failed biofeedback sessions, responded to BoNT with two patients having sustained responses for up to 1 year (Joo *et al.*, 1996). A larger study evaluating 15 patients at a dose of 25 U of BoNT injected into the external anal sphincter showed improvement in 13 patients (87%) for a mean of 4.8 months (Shafik and El-Sibai, 1998). It is unclear whether BoNT should be injected into the external anal sphincter or the puborectalis muscle. Another study evaluated 25 patients who received 10 U of BoNT on each side of the puborectalis muscle or 20 U in the posterior aspect of the muscle. Manometric relaxation was achieved after the first injection in 18 patients (75%), which endured throughout a 6-month follow-up. Seven of 16 patients who failed the first injection had an additional one. Symptom improvement of 29.2 % in straining index was recorded during follow-up with an overall satisfaction rate of 58.3% (Ron *et al.*, 2001).

Autonomic dysfunction is commonly seen in patients with Parkinson's disease, with constipation representing a frequent complaint in this group of patients (Abbott *et al.*, 2001). An initial case report described a patient with Parkinson's disease and severe outlet-type constipation who received a total of 30 U of BoNT into the puborectalis muscle. Resting anal pressures were decreased at 12 weeks, and proctography indicated improvement in the anorectal angle and evacuation of barium paste at 8 weeks (Albanese *et al.*, 1997). A follow-up study by the same group investigated 10 patients with Parkinson's disease and outlet-type constipation, receiving 100 U of BoNT into the puborectalis muscle (two sites on either side of the muscle) under transrectal ultrasonographic guidance. After treatment, anal tone during straining was reduced from  $97.4 \pm 19.6$  mm Hg at baseline to  $40.7 \pm 11.5$  mm Hg, 1-month after treatment ( $P = 0.00001$ ). A significant increase in the anorectal angle during straining was noted, and 9 patients evacuated the barium paste without the need for laxatives or enemas (Albanese *et al.*, 2003).

Rectoceles are commonly associated with outlet obstruction, such as pelvic floor dyssnergia (Maria *et al.*, 2001). Therefore, decreasing anal sphincter tone during strain may decrease the size of the rectocele and improve symptoms of constipation. In a study of 14 patients with anterior rectocele, each patient received 30 U of BoNT into 3 sites, 2 on either side of the puborectalis muscle and the third in the anterior portion of the external anal sphincter, under ultrasonographic guidance. At 2 months, 9 of 14 patients had symptomatic improvement with a decrease in rectocele depth

and area and decreased tone during straining. At one year, no patient experienced incomplete or required digitally assisted rectal voiding (Maria *et al.*, 2001).

### Summary

The use of BoNT in the treatment of pelvic floor dys-synergia is still in its infancy with only small trials supporting its use. Many questions still remain such as the dose of BoNT, location of injection, use of ultrasound or electromyography, number of treatments, and combination with biofeedback. These questions need further study using placebo-controlled trials and larger sample sizes.

### Emerging Gastrointestinal Indications

As the obesity epidemic grows in significance, novel therapeutic interventions generate great excitement. The concept of injection BoNT into the antrum of obese patients, thus causing a delay in gastric emptying and inducing early satiety, has been investigated in a few pilot trials. It has been shown in rats that injection of BoNT into the antrum can cause a decrease in food intake and subsequent weight loss (Gui *et al.*, 2000). An initial case study of one patient receiving BoNT injection into 10 areas of the prepyloric antrum had a subsequent decrease in BMI from 31.4 kg/m<sup>2</sup> to 28.6 kg/m<sup>2</sup> at 4 months. However, gastric emptying was not measured (Rollnik *et al.*, 2003). A more recent study evaluated 6 patients who received 500 U of Dysport into the antrum, with minimal, but statistically significant, decrease in weight at 4 months. However, there was no placebo arm and no evaluation of gastric emptying (Albani *et al.*, 2005). Furthermore, no changes in serum leptin and ghrelin were measurable before and after treatment. The only study to evaluate weight loss and gastric emptying did not find a change in either substance at 4 and 12 weeks after receiving 100 U of BoTN into the antrum (Garcia-Compean *et al.*, 2005).

### CONCLUSION

The use of BoNT for treatment of spastic disorders of the GI tract has gained widespread acceptance over the last 15 years, especially in the treatment of chronic anal fissures and achalasia. Its administration is generally safe and relatively non-invasive compared to many of the alternatives. However, its short-term duration of action in disorders that affect patients long-term is its most significant negative. Repeated administrations are generally necessary, with noted loss of efficacy.

BoNT administration may be most useful in "ruling in" a disorder. As in SOD and pelvic floor dys-synergia, a positive response to BoNT may indicate the

correct diagnosis and potential treatment strategies. A non-response may direct further investigations to other diagnoses. Much needs to be learned about both the mechanism of action and the long-term effects of BoNT in the unique environment of the enteric nervous system. This will further our understanding of the toxin itself as well as point to new therapeutic targets.

The use of BoNT in many GI disorders, although exciting, has not reached a level supported by clinical evidence. Further trials are needed with corresponding research to elucidate the pathophysiology of the spastic disorders of the GI tract.

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