Achalasia was one of the first gastrointestinal motility disorders to be characterized, both clinically and manometrically. Failure of relaxation of the lower esophageal sphincter (LES) is the cardinal feature of this disease, thought to result from a relatively selective degeneration of the inhibitory neurons in the surrounding myenteric plexus (Figure 1) (1-3). This leads to a functional obstruction of the esophagus that, along with aperistalsis in the body of the esophagus, is responsible for the major symptoms of achalasia: dysphagia for solids and liquids, regurgitation of undigested food and chest pain. All current methods of treatment are essentially palliative in nature and are focused on reducing the LES pressure. The main focus of this review will be on the use of botulinum toxin (BTX) for this condition and how it compares with other available therapies.

### BTX

BTX blocks the calcium-dependent release of acetylcholine from presynaptic cholinergic nerve terminals. It is a neurotoxin produced by *Clostridium botulinum*. Although several food and chest pain. All current methods of treatment are essentially palliative in nature and are focused on reducing the LES pressure. The main focus of this review will be on the use of botulinum toxin (BTX) for this condition and how it compares with other available therapies.
serotypes are known, the one used clinically is BTX type A. Pasricha et al (4) were the first to demonstrate the application of BTX for the treatment of achalasia in a double-blind, randomized, placebo controlled study. Since then, multiple studies and several reviews have been published (4-23). BTX causes a significant reduction in resting baseline LES pressure, esophageal clearance and symptoms (Figure 2). The efficacy ranges from 65% to 90% after a single injection, with the effect lasting anywhere from three months to more than one year. The main limitation to the use of BTX for achalasia is its lack of significant long term results with a single injection. With repeat injections at an average of every 10 months, Annese et al (20) recently reported the highest long term efficacy rate to date (75% after a mean follow-up of 24±15 months).

Approximately 80 to 100 U of BTX are injected endoscopically into the LES in four aliquots of 1.0 mL in each quadrant. Preliminary reports have thus far not shown a significant difference in efficacy with higher doses of BTX (17,18); more precise localization of the LES with the use of endoscopic ultrasound or injections over a wider area of the LES are similarly unproven in their effects on efficacy (20,21).

Injection of BTX appears to be safe. The most commonly reported complications are periprocedural transient chest pain and heartburn. Esophageal wall injury and paraesophageal tissue inflammation have been reported in two patients (22). Caution needs to be exercised with regard to potential, yet unknown, late side effects. Antibodies may develop against the toxin, causing resistance.

Given its low risk procedural profile, BTX injection is an attractive therapeutic option for high risk surgical patients and elderly patients, in whom conservative, albeit temporizing, management is preferred.

DRUG THERAPY

Nitrates and calcium channel antagonists have been recommended for treatment of achalasia. The rationale behind the use of these medications is their potential to decrease LES tone by relaxing gastrointestinal smooth muscle. However, the limitations in the use of these drugs are several: they are short acting; they can have significant side effects such as headaches, hypotension and tachyphylaxis; and, although a decrease in LES pressure has been well documented by manometry, symptom improvement has varied greatly among different studies (24,25). In general, most patients tend to opt for other, more satisfactory forms of treatment after they have been on these drugs for a few months.

PNEUMATIC BALLOON DILATION

Pneumatic balloon dilation has traditionally been considered the standard, first-line treatment for achalasia. Although the tools for dilation have become more sophisticated (Sir Thomas Willis treated his patient in 1672 by using a whale bone), the principle of therapy has changed little over the centuries. Multiple studies have been published on pneumatic dilation (PD) for achalasia, using different dilators (the older Mosher bag, Sippy dilators, Brown-McHardy, Rider-
longstanding postsurgical gastroesophageal reflux disease, occurring in up to one-third of the patients (28,29). Whether to perform an antireflux procedure at the time of myotomy remains controversial but is generally recommended for abdominal approaches. With the introduction of laparoscopic or thoracoscopic myotomy, surgical intervention has become more attractive because it avoids the morbidity and potential complications of a myotomy. In addition, retreatment with BTX injections may delay the need for subsequent injections.

SURGICAL MYOTOMY

Surgery has been considered the most permanent form of treatment for achalasia. Significant disadvantages include the need for hospitalization and surgical morbidity. The short term efficacy after surgical myotomy is 80% to 90%. However, late relapse, which is felt to occur in part due to long-standing postsurgical gastroesophageal reflux disease, occurs in up to one-third of the patients (28,29). Whether to perform an antireflux procedure at the time of myotomy remains controversial but is generally recommended for abdominal approaches. With the introduction of laparoscopic or thoracoscopic myotomy, surgical intervention has become more attractive because it avoids the morbidity and potential complications of a myotomy. In addition, retreatment with BTX injections may delay the need for subsequent injections.

COMPARATIVE STUDIES

Despite the abundance of literature on management of achalasia, there appears to be a relative paucity of prospective, randomized controlled studies that directly compare different treatment modalities. Until recently, there have only been two really effective methods of treating patients with achalasia: forceful dilation and surgery. Data from uncontrolled retrospective trials have, in general, suggested that success rates were higher after surgery. In a prospective, randomized, controlled trial comparing PD (using a Mosher bag) with surgical anterior esophagomyotomy, Csendes et al (32) demonstrated a five-year response rate of 65% versus 95% in clear favor of surgery.

The common limitation of PD and BTX injection is the lack of long term efficacy, with the need for repeat intervention. The literature has tried to compare the efficacy of one technique with the other. The definition of long term and short term efficacy appears arbitrary because it varies between authors. While some will define one-year follow-up data as short term, others will define a similar time span as long term. Annese et al (8) were the first to publish a randomized, controlled, double-blind study comparing BTX with placebo injections and with PD of treatment failures. One or two BTX injections appeared as effective as PD in short term relief of dysphagia. However, 87% (seven of eight) of the patients required a second injection within one year of the first injection (8). Studies published in abstract form comparing BTX with PD in a prospective, randomized manner are summarized in Table 1. Preliminary data from Bansal et al (16) suggested that the ‘short term efficacy’ (less than 12 months) of PD and BTX injections are equivalent, but initial treatment failure was significantly higher with BTX (six of 12 patients). On the contrary, Vaezi et al (19) found a significantly higher ‘long term’ efficacy (less than 12 months) with PD compared with BTX. Initial treatment failures, however, were similar for both treatment modalities in this study. Although reviews and meta-analyses clearly suggest a longer lasting effect from a single dilation than from a single BTX injection, a recent study by Prakash et al (23) using survival analysis suggested that BTX injections given as needed have an efficacy similar to a single PD within the first two years of injection. In addition, retreatment with BTX injections may delay the need for subsequent injections.

A major problem in comparative studies is the relative rarity of the disease and the difficulty in maintaining long term follow-up in patients over a five- to 10-year period. The Csendes et al (32) trial took about 15 years to complete and is unlikely to be reproduced. The debate should perhaps now be refocused, not only on efficacy of treatment regimens, but on issues of cost effectiveness and quality of life. As an example, it has been estimated that the long term (seven years) cumulative costs of surgery (approximately $20,000) are nearly two-and-a-half times more than those of PD, even taking into account the perforation rate and need for retreatment (33). A preliminary cost analysis of BTX injection, PD and laparoscopic Heller myotomy with fundoplication using decision analysis found PD to be the 'least costly initial strategy' (34).

CONCLUSIONS AND RECOMMENDATIONS

It should be clear from this brief review that the final word on treatment of achalasia is far from being written. Despite some recent advances, therapy remains palliative and each method has a significant drawback. Nevertheless, most patients can
expect to gain good to excellent symptomatic relief of their obstrucive symptoms and improvement in their quality of life. With the variety of options available, it is now increasingly possible to tailor the treatment to the needs of the patient. Thus, most young patients, desirous of a single permanent treatment, may be offered a laparoscopic myotomy with the caveat that they should be prepared for long term reflux monitoring and treatment. Others may opt for PD with good expectations from one or two dilations in the first five years. Patients fearful of perforation or those felt to be at high risk for more aggressive therapy may be given a choice of BTX injection, with the understanding that repeat injections will be required periodically.

**REFERENCES**
