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Updated Perspectives on Neurogenic Thoracic Outlet Syndrome

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Abstract Pain represents a foremost feature of neurogenic thoracic outlet syndrome (NTOS). Similar to other persistent pain conditions, the physical discomfort associated with NTOS can cause severe and often debilitating symptoms. In fact, those suffering from the syndrome report a quality of life impacted as significantly as those with chronic heart failure. This evidence-based literature review focuses on the classification, etiology, clinical presentation, diagnostic measures, and surgical treatment of NTOS, with a focus on nonoperative therapies such as physical modalities, pharmacological therapies, and more contemporary minimally invasive intramuscular treatments with botulinum toxin.

Keywords Thoracic outlet syndrome · Botulinum toxin · Scalene muscles · Pain relief · Neurogenic thoracic outlet syndrome · Brachial plexus · Computed tomography · Ultrasound · Fluoroscopy · Electromyography · Rib resection and scalenectomy · Anterior scalene muscle · Minimally invasive treatments

Introduction

Neurogenic thoracic outlet syndrome (NTOS) can produce a constellation of symptoms including ipsilateral upper extremity pain, sensory loss, shoulder and neck discomfort, arm paresis or edema, headache, and even sympathetic nervous system impairment. Often, a congenital predisposition for developing NTOS coupled with an injury leads to a compromised thoracic outlet. This narrowed space can adversely affect certain structures that lie within it, namely, the anterior and middle scalene muscles; cervical nerves of the brachial plexus, long thoracic, suprascapular, and dorsal scapular nerves; and the stellate ganglion. Though symptoms range from mild to severe, the evidence suggests that people with untreated NTOS demonstrate a quality of life that can be as impaired as those suffering from chronic heart failure [1••]. As a complex spectrum disorder, the diagnosis and treatment continue to provoke controversy [2, 3••]. Testing for NTOS with electrodiagnostics, radiographs, and magnetic resonance imaging (MRI) frequently reveals normal or nonspecific findings [4]. However, some novel, minimally invasive interventions with botulinum toxin along with surgical options may offer patients more meaningful pain relief and functional restoration. This evidence-based literature review focuses on the classification, etiology, clinical presentation, diagnostic measures, and surgical treatment of NTOS, with a focus on nonoperative therapies such as physical modalities, pharmacological therapies, and more contemporary, minimally invasive, cervicothoracic intramuscular treatments with botulinum toxin (Table 1).

Classification of Neurogenic Thoracic Outlet Syndrome

There are three basic forms of thoracic outlet syndrome: neurogenic (brachial plexus compression), arterial (subclavian artery compression), and venous (subclavian vein compression) [5] but 95% to 98% of cases are considered neurogenic [5, 6]. A subclassification of NTOS includes "true" NTOS (also known as the "classic" form with objective findings), which accounts for only 1% of neurogenic cases, and "nonspecific"

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Table 1 Overview of neurogenic thoracic outlet syndrome

Etiology [10, 58–61]	Cervical trauma (hyperextension/whiplash injury, exercise-induced scalene muscle hypertrophy, sagging shoulders), cervical rib, hypertrophied anterior scalene muscle, repetitive work-related injury, anomalous first ribs, congenitally narrowed interscalene triangle, fibrous bands
Clinical presentation [2, 4, 55]	Upper plexus (C5—C7) symptoms: ipsilateral neck or ear pain; pain in face, temple, mandible, and/or occipital areas with headaches; clavicular and pectoral pain that moves to trapezius and deltoid down lateral arm
	Lower plexus (C8–T1) symptoms: anterior and posterior shoulder pain that radiates down medial arm and forearm to hand and fourth and fifth fingers. Pain may occur in ipsilateral neck, mastoid, or occiput, causing headaches.
	General: aching, radiating down arm. Arm elevation (eg, brushing hair, working overhead, painting, housework) or carrying heavy objects exacerbates pain. Numbness, paresthesias, progressive weakness, fatigue, hand dysfunction. Symptoms may be worse at end of day; sleep disruption and cold weather worsen symptoms. Sympathetic disturbance rare: bluish-red discoloration of arm, blanching of hand.
Diagnostic measures [4, 8•, 19, 21–24]	No definitive test. Careful history and physical examinations are critical (pressure over anterior scalene muscle and supraclavicular fossa may reproduce symptoms). EAST is most reliable provocative maneuver. Electrodiagnostics, radiographs, ad MRI useful for excluding other causes (carpal or cubital tunnel syndrome, cervical disc disease, cervical ribs, shoulder problems). Anterior scalene block may be an effective confirmatory test by relaxing muscle, letting first rib to descend, and decompressing brachial plexus.
Minimally invasive therapies [8•, 17••, 27, 48, 49, 54, 62, 63]	Physical Modalities: physiotherapy, ergonomic correction, work limitations, postural correction;
	Medications: muscle relaxants, NSAIDS, TCAs, SNRIs, membrane stabilizers, opioids;
	Intramuscular cervicothoracic botulinum toxin injections: Guided by CT, ultrasound, fluoroscopy, and/or EMG. Targeting various muscles: anterior scalene, middle scalene, trapezius, pectoralis minor, spenius cervicis, supraspinatus, rhomboid major, subclavius.
Surgical Interventions [3••, 33•, 56]	Procedure and approach: first rib resection, scalenectomy, or first rib resection and scalenectomy either by supraclavicular and/or transaxillary techniques

CT computed tomography, *EAST* elevated arm stress test, *EMG* electromyography, *MRI* magnetic resonance imaging, *SNRIs* serotonin–norepinephrine reuptake inhibitors, *TCAs* tricyclic antidepressants

NTOS (also known as the "common" form, with chronic pain symptoms suggestive of brachial plexus compromise but without objective findings). The latter accounts for 99% of neurogenic cases [5]. Our discussion will encompass the "nonspecific" form of NTOS, given its predominance over "true" NTOS and vascular TOS.

Etiology of Neurogenic Thoracic Outlet Syndrome

Peet et al. [7] coined the term TOS in 1956 to describe compression of one or several neurovascular structures (brachial plexus, subclavian artery or vein) that cross the thoracic outlet [7]. The brachial plexus and subclavian vessels are vulnerable to compression as they cross three distinct areas in the cervico-axillary canal: the interscalene triangle, costoclavicular triangle, and subcoracoid space [6]. Brantigan and Roos [6] suggest that NTOS is a "space problem" due to congenital abnormalities with superimposed traumatic injury, muscle spasm, and fibrosis. Congenital anomalies such as the cervical rib and multiple types of fibrous bands can lead to brachial plexus compression with subsequent symptomatology. The incidence of cervical ribs has been reported to be 0.74% [8•]. The cervical rib and attached bands lie within the middle scalene muscle, thereby narrowing the space within the scalene triangle through which the nerve roots of the brachial plexus pass [8•]. An anatomic predisposition for developing NTOS coupled with a superimposed injury often precipitates the syndrome. Virtually any injury that causes chronic cervical muscle spasm may precipitate NTOS, such as hyperextension-flexion injuries or whiplash. For instance, the syndrome often results from neck trauma due to motor vehicle accidents, repetitive stress injury, congenital anomalies such as cervical ribs, or elements of all three [9, 10].

The anterior scalene muscle (ASM) derives from the anterior tubercles of the transverse processes of the C3–C6 vertebrae and attaches to the first rib. Functionally, the ASM acts as an accessory muscle of respiration by raising the first rib and slightly bending and rotating the neck [11]. Cervical muscle spasm involving the ASM places traction on the brachial plexus/thoracic outlet. Spasm leads to muscle edema, further limiting space in the outlet. Brantigan and Roos [6] suggest that traction leads to nerve edema, worsening the spatial dimension, and ultimately causes greater neural compromise. Moreover, scar development and fibrotic changes may complicate the problem [6], thus perpetuating the pain cycle. Accordingly, it seems reasonable

to target the ASM for treatments that relieve muscle tension and spasm, thereby preventing the cascading events that create NTOS [6].

Clinical Presentation of Neurogenic Thoracic Outlet Syndrome

NTOS occurs three to four times more frequently in women than men, and presents primarily during the third and fourth decades of life [4, 12–14]. Violinists, data entry personnel (ie, computer usage in non-ergonomic positions), and assembly line workers are particularly vulnerable given the physical nature of their occupation. Athletes who use repetitive overhead arm motion in their sport (eg, volleyball players, swimmers, baseball pitchers, and weightlifters) also may develop the syndrome, though less frequently. NTOS symptoms are aggravated by arm exertion and elevation, typically occurring after exercise rather than during exercise.

Clinical features of NTOS include a history of neck trauma and symptoms consistent with nerve irritation, such as pain, paresthesias, and weakness in the arm and hand; this most often involves all five fingers, but is more pronounced in the fourth and fifth digits and the ulnar forearm [8•]. Pain often emanates from the shoulder and radiates along the inner aspect of the arm. Patients with NTOS also may develop pain in the ipsilateral neck, trapezius, mastoid, or anterior chest wall, or complain of occipital headaches often from C5–C7 (upper plexus) compression. Many patients display symptoms that reflect compromise of the lower plexus (C8–T1). Physical exam findings include tenderness of the scalene muscles, trapezius, and anterior chest wall; a positive Tinel sign over the brachial plexus in the neck; reduced sensation to light touch in the fingers; and a positive response to provocative maneuvers that stress the brachial plexus [8•].

NTOS has been described as essentially a brachial plexus injury whereby upper plexus compression leads to an Erb-Duchenne-like palsy and typically results in lateral neck pain and hemicranial headaches, whereas lower plexus injury is likened to Klumpke's paralysis with pain in the shoulder radiating down the arm [4]. However, the entire limb is frequently involved without dermatomal preference, leading to a nonspecific clinical presentation and confounding an accurate diagnosis. This highlights the challenge of distinguishing NTOS from other upper arm pathologies including cervical radiculopathy and carpal tunnel syndrome. For instance, the symptoms of carpal tunnel syndrome typically originate in the hand and travel up the forearm, whereas NTOS discomfort usually radiates from the neck and moves down the arm to the hand. Cervical radicular symptoms from disc herniation or stenosis typically produce constant rather than intermittent pain, radiate in a dermatomal fashion, and may be reported as more severe and sharp than in NTOS.

Diagnostics

Clinical Diagnosis

There is an emphasis on the importance of a thorough history and physical examination because ancillary tests lack sensitivity or specificity [4]. Furthermore, the reliability and specificity of provocative diagnostic testing (eg, Adson maneuver, nerve tension tests) are unknown, and no test exists that is pathognomonic of NTOS [2]. Despite the diagnostic conundrum, describing differential physical examination techniques can assist the clinician with proper assessment.

In NTOS, thumb pressure held over the brachial plexus for a few seconds may reproduce the patient's neck, shoulder, and radicular pain down the arm. In contrast, the Spurling test may assist in identifying cervical disc syndrome, thereby distinguishing it from NTOS. Deep tendon reflexes tend to be normal in NTOS compared to cervical disc syndrome, which aides in localizing nerve root pathology in the latter. Some view the elevated arm stress test (EAST) [15] as the most reliable provocative maneuver for eliciting NTOS symptoms [4]. The examiner performs the EAST by abducting the patient's arm 90° in external rotation and asking the patient to open and close the hands slowly over a 3-minute period. A positive test elicits neurologic symptoms: cervical and shoulder pain, often with paresthesias that travel down the arm, forearm, and fingers [4].

In contradistinction, the Adson test is performed by evaluating changes or obliteration in the radial pulse while the patient suspends breathing, tilts the head back, and rotates the head so the chin is elevated and pointed toward the examined side. The test produces many false positive results; therefore, it is regarded as quite unreliable. For example, Rayan and Jensen [16] found that 91% of their healthy volunteers responded positively to at least one of three provocative maneuvers: the Adson's maneuver, costoclavicular maneuver, or hyperabduction maneuver. Further, a vascular response to at least one of these maneuvers was identified in 87% of cases, whereas 41% displayed a neurologic response. The vascular responses were more substantial than the neurologic responses in all three maneuvers. Thus, these maneuvers may be more helpful in assessing patients with vascular complications of TOS rather than NTOS [16]. Brantigan and Roos [4] reported that symptoms of TOS are related to brachial plexus compression and irritation rather than to vascular compression in 98% of cases.

Electrodiagnostic Studies

Electromyography/nerve conduction velocity (EMG/NCV) studies often are normal in patients with NTOS and, more importantly, can exclude other neurologic abnormalities such as radiculopathy, carpal tunnel syndrome, cubital tunnel syndrome, polyneuropathy, and motor neuron disease [8•].

Diagnostic Anterior Scalene Block

The intramuscular anterior scalene block may serve as a reliable diagnostic test for NTOS by temporarily blocking or paralyzing the muscle in spasm, allowing the first rib to descend, and thereby decompressing the thoracic outlet [13, 17••, 18, 19]. The technique was first described in 1939 and has emerged as one of the more effective tests to confirm a diagnosis of NTOS [8•, 13, 19–24]. For instance, a positive response to the block correlates well with good surgical outcomes for NTOS [21, 25]. Furthermore, Jordan and Machleder [21] showed that transient muscle relaxation offered by local anesthetic can predict who will benefit from surgical decompression. For example, electromyography (EMG)-guided injection with local anesthetic into the scalene muscle provided relief in 94% of patients who subsequently underwent surgical intervention, serving as a positive predictor for good surgical outcome. The scalene muscle injection can be performed with anatomical landmarks [22, 26], EMG [21], ultrasonography [19], EMG and fluoroscopy [27], EMG and ultrasonography [27], and most recently computed tomography (CT) [17••, 18]. Each modality offers the promise of overcoming inadvertent needle puncture or blockade of unwanted structures. For example, electrophysiologically guided needle insertion may overcome inadvertent block of somatic nerves and the brachial plexus. However, some have postulated that even this precision may not address the limitations of the test itself [4]. Current data indicate that CT guidance minimizes the rate of unwanted complications such as Horner's sign, dysphonia, brachial plexus block, and dysphagia compared to other localization techniques for scalene injections [20].

Treatment

Many treatment options for NTOS have been described in the literature, including lifestyle changes, conservative approaches, surgical approaches, and, more recently, minimally invasive treatments.

Conservative Therapy

Typically incorporated initially, conservative, nonpharmacological approaches include behavior modification, ergonomic correction, posture correction, relaxation exercises, massage therapy, nerve glides, stretching exercises, and biofeedback [28–30]. These interventions focus on decompressing the brachial plexus, restoring muscle balance in the neck, and providing neural mobility [31, 32]. If possible, patients are encouraged to seek job modification and work restrictions, such as limiting heavy lifting and avoiding repetitive, strenuous upper extremity activities, as well as adopting a slower-paced career, especially one in which they can establish their own regimen [33•].

Physiotherapy

Limited data support the use of heat packs, an exercise program, and cervical traction [34]. Inpatient rehabilitation followed by a home exercise program has been shown to produce a high percentage satisfaction rate despite methodological weaknesses in study design [32]. Finally, patients reported significant pain reduction and treatment satisfaction associated with postural correction and shoulder girdle strengthening exercises over a mean follow-up of approximately 14 months in a study by Gulbahar et al. [35]. Although some patients will improve with conservative measures, other patients with NTOS continue to develop a worsening course without further pharmacological or interventional treatments [33•]

Medications

Pharmacological strategies include muscle relaxants (eg, tizanidine), NSAIDS (eg, ibuprofen), and trigger point injections containing local anesthetic [8•]. Given the neuropathic features of NTOS (eg, radicular pain, sensory deficits, burning pain, pain attacks without provocation), both tricyclic antidepressants (eg, nortriptyline), serotonin–norepinephrine reuptake inhibitors (eg, duloxetine), and membrane stabilizers (eg, gabapentin) should be considered as adjuncts or even primary therapies for pain control. Sustained-release or long-acting opioids (eg, sustained-release morphine, oxycodone, hydromorphone; transdermal fentanyl; methadone) may be incorporated into treatment if the pain persists and quality of life is impaired despite appropriate trials of other pharmacotherapies, physiotherapy, minimally invasive therapies, or surgery.

Minimally-Invasive Approaches with Botulinum Toxin

There is a growing body of literature, including prospective clinical investigations that support the administration of botulinum toxin to the cervicothoracic musculature using disparate imaging modalities. This toxin is produced by a bacterium known as *Clostridium botulinum*, which can cause severe muscle weakness, nervous system dysfunction,

and respiratory distress if poisoning occurs [36]. Its therapeutic effects result from reducing muscle overactivity [37] and possibly decreasing pain and inflammation [38–41]. Approved uses of botulinum toxin include hemifacial spasm, blepharospasm, strabismus, cervical dystonia, glabellar lines, hyperhidrosis [42], and chronic migraine [43]. Due to its safety and clinical benefit, botulinum toxin's off-label use has expanded to ease painful conditions related to cervicothoracic muscular pain [44], lumbosacral myofascial pain [45], piriformis syndrome [46], lateral epicondylitis [47], and neurogenic thoracic outlet syndrome [17••, 27, 48, 49••]. Clinicians also have injected botulinum toxin into the cervicocranial muscles to ease hypertonic conditions such as spasmodic torticollis, achalasia, and oromandibular dystonia [50–52].

The literature demonstrates that botulinum toxin type A injection into the ASM alone, or into more than one scalene muscle along with the upper thoracic or chest wall muscles, has been effective in reducing the symptoms of NTOS. Symptomatic relief generally persists anywhere from 3 to 6 months [53•], though the average duration of pain relief calculated from five minimally invasive botulinum toxin studies is approximately 3.3 months [17••, 27, 48, 49••, 54]. Accidental spread of toxin may produce weakness, aspiration, phonation disturbance, or dysphagia. Consequently, techniques that use more precise needle targeting with lower volumes of toxin may reduce the risk of inadvertent adverse effects while permitting effective treatment for this condition. For example, Jordan and Machleder [21] found that 14 out of 22 (64%) patients with clinically diagnosed NTOS experienced greater than 50% pain reduction at 1 month with fluoroscopic and EMG-guided botulinum toxin injection into the ASM, middle scalene muscle, and the trapezius muscle versus 4 out of 22 (18%) patients who were injected with lidocaine and steroid. Furthermore, chemodenervation with botulinum toxin produced a mean duration of effect of 88 days (almost 3 months), which falls within the mean range of duration of effect on skeletal muscle [53•]. Mild transient dysphagia occurred in 2 out of 22 patients; otherwise, there were no side effects reported. Jordan et al. [27] also retrospective analyzed 77 procedures using combined ultrasound and EMG-guided botulinum toxin injections, and 168 procedures utilizing combined fluoroscopy and EMG-guided botulinum toxin injections. While 91% reported a good outcome in the ultrasound/EMG group versus 81% in the fluoroscopy/EMG group, there was no statistically significant difference in complication rates or successful outcomes between the two study populations. The authors suggested considering cost and radiation exposure before selecting which method of botulinum toxin chemodenervation to perform. Torriani et al. [19] retrospectively identified 41 patients with suspected NTOS who underwent 92 injections in total (58 ASM, 33 pectoralis minor, and 1 subclavius). A 69% rate of pain relief was noted after injection into the ASM and pectoralis minor muscle. The mean time to symptom improvement was 12 days, and mean duration of improvement lasted 31 days. While the duration of effect was less than that found in other studies [17••, 27, 48, 54], there were no reported complications. Maruo et al. [18] reported a CT-guided technique for ASM injection, which provided a fast, accurate, reliable, and safe method of needle insertion and local anesthetic delivery. Unlike using anatomic landmarks, EMG, or fluoroscopic-guidance, the benefits of CT also include the ability to visualize nearby structures that should be avoided when performing this injection. There is an added value of CT fluoroscopy, which permits real-time imaging capabilities when performing the injection. Christo et al. [17••] expanded the use of CT-guided anterior scalene injection to include the use of bupivacaine as a potential presurgical diagnostic test, and then deposited a single, low-dose amount of botulinum toxin into the muscle. The group performed a prospective longitudinal investigation on 29 procedures in 27 patients and found that patients reported significant pain reduction and minimal adverse effects for 3 months following chemodenervation of the ASM. In short, it appears that interventional techniques, especially with image or electrophysiological guidance are associated with considerably low risk and less invasiveness, and may be considered a safe alternative for the treatment of NTOS.

Surgical Approaches

Indications for surgery include at least 3 months of failed conservative therapy, disability with activities of daily living, and uncontrolled pain [33•]. Three main surgical approaches have been described: first rib resection; scalenectomy; and rib resection and scalenectomy. The first rib resection was performed by Murphy in 1908. This was followed by Adson and Coffey who introduced scalenectomy in 1927. In 1966, Roos and Owen first described the transaxillary first rib resection, which generally is performed with scalenectomy for NTOS involving C8–T1 nerve roots, or the lower brachial plexus. Since the early 1980's, scalenectomy has become a more frequent approach for NTOS that results from neck and shoulder injuries and recurrent symptoms following first rib resection. Scalenectomy often is performed for patients with compromise of the C5–C7 nerve roots, or upper brachial plexus. Since 1989, Atasoy and colleagues [33•] have combined the transaxillary first rib resection with the transcervical anterior and middle scalenectomy for total decompression of the thoracic outlet. The details of their technique are described in a recent review. Freischlag et al prefer a transaxillary approach to both the first rib resection and

anterior scalenectomy with documented improvements in quality of life measures [1••].

Data on the comparative efficacy of surgical approaches for NTOS are lacking [3••, 8•]. In fact, a recent Cochrane Collaboration review notes that very low-quality evidence supports the superiority of transaxillary rib resection over supraclavicular neurolysis of the brachial plexus for nonspecific NTOS [3••]. However, there are reports of high surgical success rates and low complication rates with surgical intervention [55, 56]. Further, a retrospective survey of outcomes on 102 patients with "thoracic outlet compression syndrome" undergoing the combined surgical approach of transaxillary first rib resection with transcervical anterior and middle scalenectomy showed that 36 patients reported 70% to 100% improvement; 24 reported 50% to 70% improvement; 26 reported 30% to 50% improvement; 9 reported 10% to 30% improvement; and 5 reported less than 10% improvement [33•]. While such data are encouraging, limitations to this study include its retrospective nature and poor follow up. It is also unclear if these patients suffered from NTOS based on history and physical examination. Interestingly, Sanders et al. [8•] reported that studies have shown no significant differences in success rate between transaxillary rib resection, supraclavicular rib resection with scalenectomy, and scalenectomy alone. However, longitudinal studies have demonstrated that approximately 60% of recurrences occur within the first year following surgery, and this increases to 80% within the second year.

Complications from surgery are not negligible. For instance, the literature reports persistent disability in 60% of patients 1 year after surgery with a complication rate that exceeds 30% [57]. Although temporary, the most frequent injury occurs to the phrenic nerve during supraclavicular operations. In fact, temporary paresis had been reported to occur in 7% to 30% of cases. Other transient nerve injuries can include the long thoracic nerve, cervical sympathetic chain, and nerve roots of the brachial plexus. Thoracic duct injury can occur from left sided neck surgery [8•].

Recently, Atasoy [33•] published complications of first rib resections performed as single procedures, which included wound infections, hematoma requiring surgical intervention, irritation of the intercostal brachial nerves (treated conservatively), pneumothorax (10%) and associated chest tube placement (less than 5%), small tears in the subclavian vein, and temporary radial nerve palsy. Among scalenectomies performed as a single procedure, complications included hematomas in the neck requiring surgical exploration and evacuation, chylus drainage treated with repeated aspiration and exploration and ligation of a lymph vessel in the neck, Horner's syndrome, and persistent dyspnea related to traction on the mobilized phrenic nerve. Several prescalene seroma formations treated with needle aspirations also were reported among cases incorporating both scalenectomy and first rib resection.

While many of the aforementioned complications were rare in Atasoy's study [33•], the complications are real and illustrate the potential for morbidity in patients undergoing surgical treatment for NTOS.

Some argue that conservative approaches yield only temporary, limited benefits and that persistently symptomatic patients require surgery if nonsurgical approaches fail [33•]. While surgical decompression can be an important and beneficial therapy, an emerging body of evidence supports a trial of minimally invasive treatments such as chemodenervation of the cervicothoracic musculature with botulinum toxin [17••, 27, 48, 49••, 54] before embarking upon operative intervention.

Conclusions

Neurogenic (nonspecific) thoracic outlet syndrome represents the most common subtype of TOS and probably causes the most detriment to quality of life [1••]. The syndrome often appears overlooked and misdiagnosed because objective findings are scarce [5, 55]. Ultimately, this leads to persistent pain, impaired function, and emotional distress. Clinical evaluation is critical to an accurate diagnosis followed by careful consultation for surgical consideration, conservative modalities, or evolving methods of minimally invasive treatments with botulinum toxin.

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