



Narrative Review: Botulinum Toxin Applications in Sports Medicine

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Abstract

Due to the botulinum toxin's (BoNT) direct and highly selective ability to induce hypotonia as well as its potential to confer potent antinociceptive efficacy, we hypothesize that there may be potential applications in sports medicine populations, which can improve pain, range of motion, and ultimately return to play. From review of the literature, we have identified four different areas of neuromuscular dysfunction for which treatment with BoNT has been shown to be effective: overactivity syndromes, muscular imbalances, bio protection, and neuromuscular pain. BoNT has emerging evidence of multiple beneficial applications in sports medicine. The evidence is strongest for plantar fasciitis and hip osteoarthritis. It is an effective and transient therapeutic option that may improve return to play times.

Introduction

Intramuscular injections of botulinum toxin (BoNT) induce muscle relaxation by blocking acetylcholinesterase at the neuromuscular junction by cleavage of synaptosomal associated protein 25 kDa (SNAP-25) [1]. There are 7 serotypes (A-G) of which only A and B are used clinically. There are four different FDA-approved therapeutic BoNTs (Onabotulinumtoxin A (BoNT-A), Abobotulinumtoxin A (AboBoNT-A), Incobotulinumtoxin A, and Rimabotulinumtoxin B (BoNT-B)). FDA-approved clinical indications include blepharospasm, cervical dystonia, chronic migraine, focal spasticity, overactive bladder, severe axillary hyperhidrosis, strabismus, and cosmetic applications (e.g. glabellar lines or wrinkles). Side effects include pain or irritation at the injection site, respiratory depression, and dysphagia. Contraindications include hypersensitivity to any preparation or components and active infection at proposed injection site. There are no known drug interactions. The onset of its effect occurs over days to weeks and generally lasts for about 3 months. Due to the toxin's direct and highly selective ability to induce hypotonia as well as its potential to confer potent antinociceptive efficacy, we hypothesize that there may be potential off-label applications in sports medicine populations, which can improve pain, range of motion, and ultimately return to play. From review of the literature, we have identified four different areas of neuromuscular dysfunction for which treatment with BoNT has been shown to

be effective: overactivity syndromes, muscular imbalances, bio protection, and neuromuscular pain.

Method

A search was conducted April 1, 2019. References for this narrative review were obtained using a search of online databases PubMed, Medline, Cochrane, and CINAHL were used to search for articles published using the terms botulinum toxin OR Botox, chemodenervation, and sports OR sports medicine. Some of the references were not identified but were obtained through reference lists of other articles. Our inclusion criteria were studies that looked primarily at sports medicine specific applications of BoNT. Eligibility of studies was assessed by 2 reviewers. BoNT is used to treat a wide variety of conditions. For clarity, we have grouped indications into the following subsections.

Overactivity syndromes

A Plantar fasciitis

Background: Plantar fasciitis is the most common cause of foot pain, affecting 10% of the US population [2,3]. Driven by the combination of repetitive opposing traction by the Achilles tendon and the forefoot windlass effect, microscopic tears occur in the central bundle of the plantar fascia [4,5]. BoNT-A injection of the calf muscles and plantar has shown some clinical promise in

easing contractures and improving symptoms in short-term studies described below. Tsikopoulos [6] compared different injection therapies for plantar fasciitis in a review of 22 trials. For pain relief, BoNT-A provided a significant short-term advantage over placebo up to 6 months. Dehydrated amniotic membrane injections were significantly superior to corticosteroids in the short-term but lacked data beyond 2 months. Recent studies have demonstrated that platelet-rich plasma (PRP) provided longer-term relief (12-18 months) for plantar fasciitis compared to corticosteroids. However, there have been no direct comparison studies of BoNT-A to amniotic membrane or PRP [7,8]. Elizondo-Rodriguez [9] performed a randomized control trial of 36 patients that compared intramuscularly applied BoNT-A in the Gastric-soleus complex with intralesional steroids for plantar fasciitis. When compared to patients who received steroids, the patients who received BoNT-A exhibited more rapid and sustained improvement over 6 months. Babcock [10] performed a randomized control trial of 27 patients (43 feet) with plantar fasciitis. Compared with placebo, the BoNT-A group significantly improved in all measures at both 2 and 8 weeks after treatment. No side effects were noted (Table1).

Table 1: Summary of recommendations based on current literature.

Pathology	Recommendation
Plantar Fasciitis	A
Chronic Exertional Compartment Syndrome	C
Functional Popliteal Artery Entrapment Syndrome	C
Lateral epicondylitis	B
Accessory Soleus Muscle	C
Runner's dystonia	C
Muscular imbalance causing knee pain	C
Piriformis Syndrome	B
Shoulder impingement	B
Rotator Cuff Repair Immobilization	B
Increasing Dorsiflexion after Achilles Tendon Repair	C
Osteoarthritis: Hip/Knee	I
Whiplash Associated Disorder	I

Conclusion grade A recommendation: There is level I evidence that BoNT can improve pain and function in patients with plantar fasciitis.

B Chronic exertional compartment syndrome (CECS)

Background: Chronic exertional compartment syndrome is characterized by compartment pain triggered by exercise and abnormally high compartment pressure after exercise. The pathophysiology is due to discrepancy between muscle size and its constricting fascial compartment, muscle ischemia, or stimulation of local nociceptors. Given a proposed role of muscle hypertrophy, BoNT-A could help in the management of CECS by reducing the volume of the compartment content. Baria [11] presented a case with continued pain relief after AboBoNT-A and had resumed her

active lifestyle without any adverse effects up to 14 months. In a case series by Isner-Horobeti [12], AboBoNT-A was injected into the muscles of 16 moderately trained patients diagnosed with anterior or anterolateral exertional compartment syndrome of the leg (25 anterior compartments and 17 lateral compartments). At 9-month follow, the exertional pain was eliminated in 15 patients. In 5 patients, the strength of the injected muscles remained normal. In 11 patients, strength decreased significantly from 4.5 (1 month after the first injection) to 3.5 (at final follow up), although without functional consequences.

- **Conclusion-grade C recommendation:** There is level IV-V evidence that BoNT can improve pain in patients with CECS without functional strength loss up to 9-14 months.

C Functional popliteal artery entrapment syndrome

Background: Functional popliteal artery entrapment syndrome (FPAES) is notable cause of exercise-induced muscle leg pain that is often due to the increased bulk of the gastrocnemius muscles [13]. proposed mechanisms of action for intramuscular periarterial BoNT therapy for FPAES are [14] 1) paralysis and/or localized atrophy of the muscle responsible for the dynamic arterial occlusion, and 2) possible arterial smooth muscle relaxation of the popliteal artery resulting in vasodilatation. Murphy [15] published a case report regarding an elite male athlete with FPAES. The athlete experienced a decrease in strength and performance at 1-week post-injection but returned to baseline within four weeks. The athlete had an increase in his sprint distance per game post-injection. On ultrasound, he had visible medial gastrocnemius denervation atrophy with a decrease in arterial flow velocity at four weeks post-injection. Hislop [16] published a case series of 27 patients that received ultrasound-guided BoNT-A injection at the level of artery occlusion. No patients reported being worse off after the intervention; 59% of patients had a good response (initial improvement maintained at 12 months), 22% a mixed response (initial improvement that reduced over 12 months), and 19% a poor response (no difference) to treatment. Isner-Horobeti [17] published a case of a soldier with bilateral functional popliteal artery entrapment syndrome that did not improve after bilateral popliteal arteriolysis without resection of the gastrocnemius medial head. After AboBoNT-A, follow-up (from 1 month to 3 years after BoNT treatment) showed disappearance of exercise-induced pain and improvement of the physical and sports performance.

Conclusion - grade C recommendation: There is level IV-V evidence BoNT can improve symptoms of FPAES however, athletes may experience a transient decrease in function.

D Lateral epicondylitis

- **Background:** lateral epicondylitis refers to pain in the lateral elbow due to repetitive wrist Oskarsson [18] demonstrated low intramuscular blood flow in the extensor carpi radialis brevis (ECRB) in patients with lateral epicondylitis, postulating that mechanism of injury is due to decreased microcirculation from persistent muscle contraction. Anaerobic metabolism would subsequently cause lactate accumulation and muscle swelling.

Therefore, muscle relaxation induced by BoNT may improve microcirculation and swelling. Creuze [19] performed a randomized control study of 60 patients with chronic lateral epicondylitis resistant to treatment for >6 months. Pain intensity and the effect on quality of life were both significantly lower in the group treated with AboBoNT-A compared with placebo at day 90. The rate of clinically detected transitory paresis of the third finger on extension was 17.2% in the AboBoNT-A group without functional impairment. Lian [20] performed a systematic review of 36 randomized control trials. BoNT improved pain at mid-term follow up. All treatments increased adverse events compared with placebo. 92% of patients experienced pain resolution after receiving placebo within 4 weeks of follow-up. Dong's [21] systematic review demonstrated a significant difference between BoNT and placebo by the pairwise meta-analysis results but became non-significant during network meta-analysis. Krogh [22] performed a systematic review of 17 trials to assess the comparative effectiveness and safety of injection therapies in patients with lateral epicondylitis. Although BoNT showed marginal benefit, it caused temporary paresis of finger extension, and all trials were at high risk of bias. Oskarsson [23] published a case series of 10 patients with unilateral epicondylitis and decreased intramuscular blood flow in ECRB. The difference in intramuscular blood flow between the control and the affected side had decreased 3 and 12 months after AboBoNT-A. Lactate concentration at the 12-month follow-up had decreased while perceived pain was reduced and function in daily activities had improved.

- **Conclusion - Grade B Recommendation:** There is level I-IV evidence that BoNT-A can improve pain in lateral epicondylitis, however, care must be taken to avoid paresis of the third finger.

E Accessory soleus muscle

- **Background:** Symptomatic accessory soleus muscle (ASM) can cause exercise-induced leg pain due to local nerve/vascular compression, muscle spasm, or local compartment syndrome. As intramuscular injections of BoNT-A can reduce muscle tone and mass, it may alleviate symptomatic ASM. Isner-Horobeti [24] published a case series of 5 patients. After BoNT-A injection, exertional pain disappeared, and all five patients resumed their normal level of physical and sports performances. Neither side effects nor motor deficits were observed.

- **Conclusion - Grade C Recommendation:** There is level IV evidence that BoNT-A is well tolerated and can improve pain in patients with ASM for years after treatment.

F Task-specific dystonia: runner's dystonia

- **Background:** Task-specific dystonias seen in sports medicine include Runner's dystonia and golfer's yips [25]. Task-specific movement disorders constitute a group of hyperkinetic movement disorders that occur only during certain activities, postures, or circumstances such as a writer's cramp. BoNT has provided symptom relief through relaxation of the affected muscle. The retrospective case series by Ahmad [26] presented surface electromyography (EMG) and joint kinematic data from 13 patients with RD who underwent instrumented gait analysis

(IGA) for muscle selection for BoNT therapy. Nine patients received BoNT therapy based on the results of IGA, and 7/9 reported some benefit. Three patients reported significant benefit allowing them to continue long-distance running. The remaining four patients reported variable levels of benefit, allowing some to continue training at lower intensity levels while others reported only a short-lived treatment response. Two patients had no response to BoNT at high doses. The retrospective review of 20 patients with runner's dystonia by Cutsforth-Gregory [27] found that BoNT, levodopa, clonazepam, trihexyphenidyl, and physical therapy provided modest benefit to some, but all patients remained substantially symptomatic at last follow up (up to 4.2 years after diagnosis). The case series of 5 patients by Wu [28] examined the effects of BoNT on the dystonia of 1 leg during long-distance running. One patient benefited from an oral anticholinergic, 1 from levodopa, and 2 patients benefited from repeat BoNT injections.

- **Conclusion - Grade C Recommendation:** There is level III-IV evidence that BoNT-A can improve symptoms in patients with runner's dystonia.

Muscular imbalances

A. Anterior knee pain

- **Background:** Muscle overactivity in neurologically normal muscle, where an imbalance exists between a relatively overactive muscle and its less active synergist or antagonist, can inhibit control of the antagonist producing a functional muscle imbalance [29]. Intramuscular injection of BoNT has the potential to correct imbalances by the reduction of focal muscle overactivity and localized muscle spasm. The case series of 45 patients by Stephen [30] investigated the effect of an ultrasound-guided AboBoNT-A injection into the tensor fasciae latae, followed by physical therapy, in patients classified with lateral patellofemoral overload syndrome who failed to respond to conventional treatment. There was a significant improvement in Anterior Knee Pain Scale (AKPS) scores from before the injection to 1, 4, and 12 weeks after the injection and in 87% of patients at approximately 5 years after the injection. A significant effect on the modified Ober test was identified as a result of the intervention, with an increase in leg drop found at 1, 4, and 12 weeks after the injection compared with before the injection.

The randomized controlled crossover trial by Singer [31] examined the efficacy of AboBoNT-A injection plus an exercise program to remediate chronic anterior knee pain associated with quadriceps muscle imbalance in 24 patients. The injection targeted the vastus lateralis with the intention of disinhibiting the vastus medialis. Improvement at 12 weeks was significantly greater for BoNT-A compared with placebo-injected subjects for the AKPS, pain on kneeling, squatting and level walking. At 24 weeks, 16 of 19 BoNT-A-injected and 2 of the remaining 5 placebo-injected subjects were either satisfied or very satisfied with treatment outcomes. Improvements were maintained in 11 of 14 BoNT-A-injected and 2 of 5 placebo subjects available at longer-term follow-up. A follow up study demonstrated that improvements were sustained at follow-up, with an average benefit of 34 months post-injection in

44/57 cases. Cullen [32] presented two cases with improved pain functional muscle balance. After two weeks, one case was able to produce an isolated gluteal muscle contraction after receiving 500 units of AboBoNT-A in her left upper hamstrings. The second case had relief after two injection episodes of AboBoNT-A into the distal vastus lateralis and tensor fascia latae.

• **Conclusion - grade C recommendation:** There is level IV evidence that intramuscular injection of BoNT, in carefully selected cases, provides short term reduction of focal muscle overactivity, and may facilitate activation of relatively 'inhibited' muscles and assist the restoration of more appropriate motor patterns (Table 2-a-c)

Table 2: Summary of evidence based on current literature (new to old). U = units of Onabotulinum toxin-type A unless specified otherwise.

Nociception					
Pathology	Author	Design	Protocol	Results	Evidence
Osteoarthritis	Eleopra [41]	Randomized, Double-Blinded, Placebo-Control	400U AboBoNT-A into adductor muscles	4-week Harris Hip Score & VAS significant improvements	I
	Hassan [42]	Systematic review, nonhomogenous		Limited supporting evidence	II
	Mahowald 2016	Case series	25-50U in 3 knees and 3 ankles and 450-100 units in 9 shoulders	Significant 55% decrease in lower extremity pain, 36% improvement in Timed Stands Test, 71% reduction in shoulder pain, active range of motion increased in flexion 67% and abduction 42%	IV
				Duration of pain relief 3-12 months	
Whiplash	Teasel [44]	Systematic Review - nonhomogenous	3 RCTs & 1 case series	Contradictory evidence during chronic stage (>12 weeks after injury)	II
	Braker [45]	Randomized, Double-Blinded, Placebo-Control	20 patients with cervical myofascial pain 2-48 weeks after whiplash who had 200U into 4 tender points	Greater percentage of patients who received BoNT achieved a 50% reduction in pain intensity at 24 weeks but more adverse effects	I
	Padberg [46]	Randomized, Double-Blinded, Placebo-Control	40 patients with grade 1-2 whiplash received 100U into muscles with increased tenderness	At 12 weeks, no significant difference	I
	Juan [47]	Randomized, Double-Blinded, Placebo-Control	5 injections of 20U into 1 or more of: splenius capitis, semispinalis capitis, trapezius	No final data	I
	Freund 2002	Randomized, Double-Blinded, Placebo-Control	28 patients with chronic grade 2 WAD 100U AboBoNT-A or saline in splenius, capitis, rectus	Significant reduction in pain at 4 weeks	I

Table 2a.

Overactivity Syndromes					
Pathology	Author	Design	Protocol	Results	Evidence
Plantar Fasciitis	Tsikopoulos [6]	Systematic review & network meta-analysis of 22 randomized controlled trials		Provided significant short-term advantage over placebo that was still present at 6 months	I
	Elizondo-Rodriguez [9]	Randomized, Double-Blinded, Placebo-Control	100U each medial & lateral gastrocnemius & 50U soleus	Rapid & sustained improvement compared to steroids over 6 months	I
	Babcock [10]	Randomized, Double-Blinded, Placebo-Control	70U divided into 2 sites per foot	Improved pain and function at 3- and 8-week follow up	I

Chronic exertional compartment syndrome (CECS)	Baria [11]	Case report	20U AboBoNT-A proximally & 20U distally in the following on the left leg: Tibialis anterior, extensor hallucis longus, extensor digitorum longus, fibularis longus, fibularis brevis	Pain decreased to 1/10 from 9/10 in 1 week	V
				jogging short distances w/in 2 weeks	
				1 month increased to 2-3 miles several times/weeks	
				14 months: no further pain, symmetric leg circumference & normal strength	
	Isner-Horobeti [12]	Case series	25 anterior compartments & 17 lateral compartments injected with AboBoNT-A	Decreased intramuscular pressure & eliminated exertional pain up to 9 months	IV
Functional Popliteal Artery Entrapment Syndrome (FPAES)	Murphy [15]	Case Report	50U medial gastrocnemius heads bilaterally	1 week decrease in strength & function	V
				Ceased lower body exercise for 1 week & gradual return to training over 2 weeks	
				Beneficial effect on pain during sport	
	Hislop [16]	Case Series	27 patients injected at level or artery occlusion	4-week decrease in peak arterial velocity & increase in vessel size	IV
0% no worse off					
59% good response					
22% mixed					
	Isner-Horobeti [17]	Case report	400U of AboBoNT-A in proximal third of medial & lateral gastrocnemius bilaterally	19% no response	V
No pain after 1 month					
2.5 months no compromise in blood flow					
	Creuze [19]	Randomized, Double-Blinded, Placebo-Control	60 patients 40U AboBoNT-A vs saline into ECRB	4 months - return to sport without issues	I
3-month follow up: 51.7% reported >50% reduction in initial pain intensity					
Pain intensity & effect on quality of life significantly lower					
	Lian [20]	Systematic Review & Meta-analysis of Randomized Placebo-Controlled Trials	3 studies, 237 patients for BoNT	Transitory paresis of 3rd finger on extension 17.2% in BoNT-A group	I
				5-26 weeks number needed to treat (NNT) pain relief 18 (14-31)	
	Dong [21]	Systematic review & Bayesian network meta-analysis		Botulinum toxin better than placebo and corticosteroid injection	I
	Krogh [22]	Systematic Review & Network Meta-analysis of Randomized Controlled Trials	4 trials assessing BoNT	Marginal pain benefit, caused temporary paresis of finger extension, all trials high risk of bias	I
	Oskarsson [23]	Case series	1U/kg AboBoNT-A injected 2 fingerbreadths distal to lateral epicondyle, upper dose limit of 100U/muscle	Improves intramuscular blood flow, aerobic metabolism, functional activity, and relieves pain at 12-month follow up	IV
Accessory Soleus Muscle	Isner-Horobeti [24]	Case Series	280-1000U injected	Disappearance of exertional pain and resumption of normal activity up to 10 years after injection	IV

Task-specific dystonia	Ahmad [26]	Retrospective case series	Runner's dystonia 13 patients	7/9 received benefit	IV
	Cutsforth-Gregory [27]	Retrospective review	20 patients (13 runners, 7 non-runners)	Beneficial in 4/7 patients	III
	Wu 2006	Case series	Runner's dystonia, 5 cases	2 patients benefited	IV

Table 2b.

Muscular Imbalance Syndromes					
Pathology	Author	Design	Protocol	Results	Evidence
Anterior Knee Pain	Stephen [30]	Case series	Ultrasound -guided AboBoNT-A injection into tensor fascia latae with physical therapy	Significant improvement in Anterior Knee Pain Scale Score up to 5 years	IV
	Singer [31]	Case series	500U AboBoNT-A in vastus lateralis	Improvement at 12 weeks based on Anterior Knee Pain Scale Score	IV
	Cullen [32]	Review & case series	1) 500U AboBoNT-A to L upper hamstrings	1) Isolated gluteal muscle contraction in 2 weeks	IV
			2) 180U in distal third of vastus lateralis & 120U to tensor fascia latae with repeat of 500 into each after 5 months	2) Improved pain & activity progression at 2 weeks with pain after return to full weight bearing. With second injection, improved pain and able to return to play.	
Piriformis Syndrome	Yoon [35]	Prospective, case control	150U AboBoNT-A injected by CT-guidance into piriformis	Significant reductions in pain at week 4,8, and 12	II
	Lang [36]	Case series	Piriformis injected once with 5000U of BoNT-B under EMG-guidance	Significant reductions in VAS for buttocks & hip pain at weeks 4,12, and 16 and for low back pain at weeks 2, 12, and 16	IV
Rotator Cuff Impingement	Lin [37]	Systematic Review, Pairwise & Network Meta-analysis of Randomized Controlled trials		Ineffective for rotator cuff tendinopathy	I
	Lee [38]	Case series	2500U BoNT-B subacromial bursa vs triamcinolone	At 3 months, BT decreased NRS and DASH & greater shoulder abduction than triamcinolone	IV

Table 2c.

Bioprotection					
Pathology	Author	Design	Protocol	Results	Evidence
Rotator cuff repair	Gilotra [39]	Rat model	84 supraspinatus tendons injected w/ saline or examined at 2, 4, 8, and 12 weeks	May help protect repair but cast immobilization plus BoNT administration was harmful to healing	II
Achilles tendon repair	Reuter [40]	Case series	200-300U in gastrocnemius & soleus	2 years improved pain and dorsiflexion of 21 degrees reached	IV

B Piriformis syndrome

• **Background:** Piriformis syndrome is caused by prolonged or excessive contraction of the piriformis muscle associated with pain in the buttocks, hips, and lower limbs because of the close proximity to the sciatic nerve. BoNT-A reduces muscle hypertonia as well as muscle contracture and pain inhibiting substance P release and other inflammatory factors [33,34]. The prospective study by Yoon [35] evaluated the efficacy of a single, low-dose injection of AboBoNT-A in 29 patients. Pain intensity scores were significantly lower at 4, 8, and 12 weeks after treatment than at baseline. Four weeks after treatment, physical functioning, bodily pain, general health, vitality and social functioning improved significantly from baseline. The prospective study by Lang [36] evaluated the clinical safety and efficacy of BoNT-B in reducing myofascial pain associated

with piriformis syndrome in 20 patients. Significant reductions in mean visual analog scale scores for buttock and hip pain were noted at weeks 4, 12, and 16 and for low back pain at weeks 2, 12, and 16. Visual analog scale scores for general and low back pain, pain radiating into lower limbs, and tingling were significantly lower at week 2 after injection, suggesting early onset.

• **Conclusion - Grade B Recommendation:** There is level II-IV evidence that BoNT can improve pain attributed to piriformis syndrome.

C Rotator cuff impingement

• **Background:** Rotator cuff impingement occurs when the myotendinous junction of the supraspinatus tendon comes into contact with either the undersurface of the acromion, a subacromial

spur or an enlarged acromioclavicular joint. BoNT has potential to alleviate shoulder impingement syndrome by decreasing muscle overactivity. Lin [37] published a pairwise and network meta-analysis of 18 studies to compare effectiveness of injection therapies in rotator cuff tendinopathy. The randomized prospective study by Lee [38] examined 61 patients treated with BoNT-B (BT group) or triamcinolone injection (TA group) under ultrasound guidance. Both groups obtained a significant improvement of Numeric Rating Scale, Disability of Arm, Shoulder, and Hand, and active shoulder abduction at 1 and 3 months follow-up. BT group showed significantly better outcomes in terms of reduction of NRS and DASH at 3 months than TA group. BT group showed strong trend toward the larger degree of active shoulder abduction than the TA group at 3 months follow-up, as well.

- **Conclusion - grade C recommendation:** There is level IV evidence that BoNT can improve pain in patients with rotator cuff external impingement.

Bio protection

A Rotator cuff repair

- **Background:** Increased postoperative activity is a risk factor for impaired rotator cuff repair. Various protocols of immobilization have been recommended but not substantiated to allow the rotator cuff to heal without jeopardizing long-term range of motion. Because of patient compliance issues and biological challenges, optimizing the postoperative healing environment remains difficult. As BoNT causes temporary muscle paralysis, it may have a role in facilitating postoperative immobilization. Gilotra [39] evaluated the effects of BoNT-A and cast immobilization on tendon healing in a rat model. Eighty-four supraspinatus tendons were surgically transected and repaired in 42 Sprague-Dawley rats. After repair, supraspinatus muscle was injected with saline or BoNT-A. Half the shoulders were cast-immobilized for the entire postoperative period; half were allowed free cage activity. Botox alone and cast immobilization alone exhibited increased ultimate load compared with at 4 weeks. No difference in ultimate load occurred between Botox-only and cast-only groups. At 12 weeks, the Botox plus cast immobilization group was significantly weakest. A trend was shown toward decreased healing zone cross-sectional areas in casted groups (Table 3).

- **Conclusion-Grade B:** There is level II evidence that supraspinatus Botox injection after rotator cuff repair can help protect the repair. However, prolonged immobilization plus Botox administration proved harmful to rotator cuff healing in a rat tendon model.

B Achilles tendon repair

- **Background:** Although outcome after surgical repair of complete Achilles tendon rupture is good, some patients have ongoing problems with dorsiflexion of the ankle joint. Reuter [40] analyzed a case series of 8 patients with reduced ankle dorsiflexion 5 months after surgical repair of complete Achilles tendon rupture. All patients received at least 3 cycles of injections with 200–300 units of BoNT-A into the gastrocnemius and soleus muscle.

Weakening of the triceps sure by BoNT allowed patients to perform the required exercises and to tolerate casting at night. All patients were able to tolerate plantigrade foot position 9 months after beginning of BoNT treatment. At final follow-up after 2 years, pain had significantly improved, and a mean dorsiflexion of 21 degrees was reached.

- **Conclusion-Grade C recommendation:** There is level IV evidence that the BoNT can improve restricted dorsiflexion in patients after Achilles tendon repair.

Nociception

A Osteoarthritis

- **Background:** BoNT has been suggested to have an antinociceptive effect when applied to painful joints by blocking neurotransmission from nerve terminals of nociceptive fibers. The randomized control study by Eleopra [41] AboBoNT-A injections (400 units into adductors) versus placebo (1.6mL saline) to improve hip range of motion, pain and quality of life in patients with hip osteoarthritis. At Week 4, the Harris Hip Score (HHS) and Visual Analog Score (VAS) were significantly improved compared to the placebo. No significant changes were observed in muscle strength and quality of life. The review by Hassan [42] evaluated 18 studies demonstrating limited evidence for BoNT-type A in knee osteoarthritis. The control group in several studies included did not have a control. Therefore, due to the possibility of placebo effect and bias could not be eliminated. The case series by Mahowald followed eleven patients for 12 months after intra-articular injections of BoNT-A for refractory joint pain due to osteoarthritis, rheumatoid arthritis and psoriatic arthritis. For the lower extremity joints (knee and ankle), the mean maximum decrease in joint pain was 55% and the 36% improvement in the Timed Stands Test was noted at 4 to 10 weeks after injection. For the upper extremity (shoulder), there was a 71% mean maximum reduction in pain severity and active range of motion increased 67% in flexion and 42% in abduction. Duration of pain relief ranged from 3 to 12 months [43].

- **Conclusion**

- i. **No Recommendation (hip):** There is 1 study of level I evidence that BoNT may improve range of motion and pain in hip osteoarthritis after BoNT- A injection into the adductors. If there were studies examining hip intraarticular injections of BoNT-A injections, the outcomes may be similar to knee osteoarthritis.

- ii. **No Recommendation (knee):** There is insufficient evidence BoNT-type A injections may help pain related to knee osteoarthritis. As there has been evidence of pain improvement after BoNT-A injections in the periarticular hip musculature, there may be avenues of pain improvement for patients with knee osteoarthritis by injecting BoNT-A injections into the periarticular knee musculature. The pain-relieving mechanism of action may be similar to those described in the muscular imbalances and overactivity sections.

Whiplash

- **Background:** Whiplash associated disorder is commonly linked to motor vehicle accidents and sports injuries. Cervical

injury is attributed to rapid extension followed by neck flexion. The exact pathophysiology of whiplash is uncertain but is suspected to involve aberrant muscle spasms causing a wide range of pain symptoms. BoNT is a proposed treatment to relieve the aforementioned symptoms by muscle relaxation. Teasel [44] reviewed 3 randomized controlled trials and 1 case series on the effect of BoNT-A injections in the treatment of chronic whiplash-associated disorder (WAD). Patients who received BoNT injections achieved greater and longer-lasting pain relief as well as improved

range of motion but not enough to achieve significance. The randomized controlled trial by Braker [45] followed 20 patients with cervical myofascial pain 2-48 weeks after a whiplash injury. The patients received either 200 units of BoNT-A or equal volume of saline injected equally into 4 trigger points. Although the BoNT-A group consistently made larger improvements, between-group differences were nonsignificant with the exception that a greater percentage of patients in the BoNT-A group achieved a 50% reduction in pain intensity at 24 weeks (Table 3).

Table 3: Levels of Evidence.

Evidence	Types of Studies			
	Therapeutic	Prognostic	Diagnostic	Economic and Decision Analysis
	Investigating the results of treatment	Investigating the effect of a patient characteristics on the outcome of disease	Investigating a diagnostic test	Developing an economic model or decision model
Level I	High-quality randomized trial with statistically significant difference but narrow CIs			
Systematic review of level I RCTs (and study results were homogenous)	High-quality prospective study (all patients were enrolled at the same point in their disease with ≥ 80% follow-up of enrolled patients) Systematic review of level I studies	Testing of previously developed diagnostic criteria on consecutive patients (with universally applied reference “gold” standard) Systematic review of level II studies	Sensible costs and alternatives; values obtained from many studies; with multiway sensitivity analyses Systematic review of level I studies	
Level II	Lesser-quality RCT (e.g., < 80% follow-up, no blinding, or improper randomization) Prospective comparative study Systematic review of level II studies or level I studies with inconsistent results	Retrospective study Untreated controls from an RCT Lesser-quality prospective study (e.g., patients enrolled at different points in their disease or < 80% follow-up)	Development of diagnostic criteria on consecutive patients (with universally applied reference “gold” standard) Systematic review of level II studies	Sensible costs and alternatives; values obtained from limited studies; with multiway sensitivity review Systematic review of level II studies
Level III	Case-control study Retrospective comparative study Systematic review of level III studies	Case-control study	Study of nonconsecutive patients; without consistently applied reference “gold” standard Systematic review of level III studies	Analyses based on limited alternatives and costs; poor estimates Systematic review of level II studies
Level IV	Case series	Case series	Case-control study Poor reference standard	Analyses with no sensitivity analyses
Level V	Expert Opinion	Expert Opinion	Expert Opinion	Expert Opinion

The randomized controlled trial by Padberg [46] followed 40 patients with chronic WAD who received either 100 units of BoNT-A or 2 mL. After 12 weeks, no significant differences in pain intensity or cervical range of motion were found between the 2 groups. Juan published a case series [47] 31 patients with WAD for ≥3 months refractory to conservative treatment. A dose of 50 to 75 units of BoNT-A was injected into each patient’s tender superficial muscles. Patient were also provided with a home exercise program. 77.4% of patients responded positively to the treatment. Significant improvements were seen in terms of both pain intensity and cervical ROM. In the randomized controlled trial by Freund, 30 patients

with WAD for ≥6 months refractory to conservative treatment who received 100 units AboBoNT-A or 1 mL saline delivered to the 5 most tender cervical trigger points. At 4 weeks, patients in the treatment group had better cervical ROM, and less neck, head and shoulder pain than those in the placebo group.

- **Conclusion** - No Recommendation: There is currently insufficient evidence for the treatment of WAD with BoNT. However, there is evolving evidence that BoNT may be helpful for pain management, but studies thus far have not reached significance (Table 4).

Table 4: Grades of Recommendation.

Grade	Description
A	Good evidence (Level-I studies with consistent findings) for or against recommending intervention
B	Fair evidence (Level-II or III studies with consistent findings) for or against recommending intervention.
C	Conflicting or poor-quality evidence (Level-IV or V studies) not allowing a recommendation for or against intervention.
I	There is insufficient evidence to make a recommendation.

Conclusion

BoNT has emerging evidence of multiple beneficial applications in sports medicine. The evidence is strongest for plantar fasciitis and hip osteoarthritis. It is an effective and transient therapeutic option that may improve return to play times.

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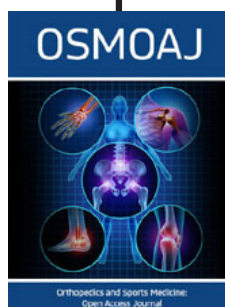
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