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Intra-articular injection of botulinum toxin type A for shoulder pain in glenohumeral osteoarthritis: a case series summary and review of the literature

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Nicoletta Cinone[1]
Sara Letizia[1]
Luigi Santoro[1]
Michele Gravina[2]
Loredana Amoruso[1]
Franco Molteni[3]
Maurizio Ranieri[1]
Andrea Santamato[1,4]

[1]Physical Medicine and Rehabilitation Unit, Ospedali Riuniti, Università di Foggia, Foggia, [2]Rehabilitation Center, "Padre Pio" Foundation, San Giovanni Rotondo, [3]"Villa Beretta" Rehabilitation Unit, Lecco, [4]Rehabilitation Center, "Turati" Foundation, Vieste, Italy

Introduction: Shoulder pain is one of the most common musculoskeletal diseases, and can be due to glenohumeral osteoarthritis, rotator cuff tear, impingement, tendinitis, adhesive capsulitis, and subacromial bursitis. Several therapies have been proposed, including steroids, nonsteroidal anti-inflammatory drugs, intra-articular injections, and physical therapies. Many published studies have reported on the employment of botulinum toxin type A (BoNT-A) to reduce pain in subjects with neurological and musculoskeletal diseases by inhibiting substance P release and other inflammatory factors.

Methods: In the present article, we briefly update current knowledge regarding intra-articular BoNT therapy, reviewing existing literature on intra-articular use of BoNT-A, including nonrandomized and randomized prospective and retrospective cohort studies and case series published from December 1989 to November 2017. We also describe a case series of six subjects treated with intra-articular injection of incobotulinumtoxin A for the treatment of pain deriving from osteoarthritis.

Conclusion: Intra-articular BoNT-A is effective and minimally invasive. Pain reduction with an increase in shoulder articular range of motion in our experience confirms the effectiveness of BoNT-A injection for the management of this syndrome.

Keywords: shoulder-pain syndrome, botulinum toxin type A intra-articular injections, glenohumeral osteoarthritis

Introduction

Shoulder pain is one of the most common musculoskeletal complaints in modern societies, second only to low-back pain in patients seeking care for musculoskeletal disorders in the primary-care setting.[1] Prevalence is uncertain, with estimates of 4%–26%.[2] Although more than half of all patients with shoulder pain recover completely within 1 year, the remaining report persistent shoulder pain. Pain and shoulder-function impairment may lead to social and personal inability affecting health care costs, including absence from work and disability.

Shoulder pain has several underlying etiologies, including glenohumeral osteoarthritis, rotator cuff tear (full or partial), impingement, tendinitis, adhesive capsulitis, and subacromial bursitis.[3] The most common source of shoulder pain is the rotator cuff, accounting for over two-thirds of cases.[2] The use of intramuscular botulinum toxin type A (BoNT-A) injection to address focal muscle overactivity is well established in the management of spasticity,[4] but there is an increasing body of evidence to support a role in the field of pain modulation.[5,6] The effect was first proven in the treatment of cervical dystonia, associated pain spasticity, migraine, and tension-type headache, and

Correspondence: Andrea Santamato
Physical Medicine and Rehabilitation Unit, Ospedali Riuniti, Università di Foggia, Via Vittime Civili Viale, Pinto, Foggia 71100, Italy
Tel +39 881 736 258
Fax +39 881 732 564
Email andrea.santamato@unifg.it

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mostly with intramuscular injection.[7–9] There has been limited published literature relating its intra-articular application, and dosing also remains an area for discussion.

The primary objective of the present paper was to conduct a literature review focused on existing evidence on intra-articular BoNT-A injections. In addition, we report a case series clinical experience to evaluate the effect of intra-articular BoNT-A on shoulder-pain relief and function in patients with persistent shoulder pain due to osteoarthritis. Safety and tolerability were also evaluated.

Methods

We reviewed existing literature on intra-articular use of BoNT-A, including nonrandomized and randomized prospective and retrospective cohort studies and case series published from December 1989 to November 2017. The search was conducted in PubMed, Ovid Medline, Embase, Google Scholar, Web of Science, and Scopus using the primary search terms or their synonyms (individually and in combination) "intra-articular", "shoulder", "knee", "ankle", "osteoarthritis", "joint", and "botulinum toxin, BTX, or BoNT". Any joint was included, with no restriction. A search filter was developed to include only human studies. We only included articles in which pain originated from bones and joints. Case reports were not included in this review. There were no language restrictions on search. The references of all selected studies were screened to identify studies that had not been included in the electronic search. At first check, we identified 136 articles, of which only seven were considered eligible. We obtained the full texts of the related articles and selected the most eligible articles for the review.[10–16] All the articles included are shown in Table 1.

Intra-articular use of BoNT-A

The first clinical study related to intra-articular BoNT-A for pain was by Mahowald et al in 2006. The authors evaluated the efficacy of BoNT-A for management of moderate–severe refractory joint pain. Eleven patients with chronic arthritis who had failed treatment with oral and/or intra-articular medications and with no indication for surgery were injected intra-articularly with 25–100 U BoNT-A in knee joints, ankle joints, and shoulder joints. The mean maximum decrease in pain after the first intra-articular BoNT-A injection was 55% for lower-extremity joints and 71% for shoulder pain. In long-term follow-up, joint-pain reduction lasted 3–12 months from the first injection and 3–8 months after repeated injections, with a global improvement in limb function and quality of life.[10]

In a randomized controlled trial, Singh et al evaluated the efficacy of intra-articular BoNT-A 100 U versus placebo in 36 subjects with refractory shoulder pain due to osteoarthritis. The main outcome measure was change in pain severity (measured with visual analog scale [VAS]), and secondary outcome measures were functional impairment and disability assessed using the Shoulder Pain and Disability Index, active range of motion (ROM) measured using goniometry, quality of life assessed using the SF36, and the sensory and affective dimensions of pain according to the short version of the McGill Pain Questionnaire. Improvement in pain severity and quality of life (measured with SF36) following intra-articular BoNT-A injection was significantly greater than placebo: 1 month after a single injection, 61% of patients had 30% or ≥2-cm decrease in pain severity.[11]

In a randomized double-blind pilot study conducted on 60 patients with painful osteoarthritis of the knee, patients were stratified to receive intra-articular corticosteroid, low-dose BoNT-A (100 U), or high-dose BoNT-A (200 U). Pain VAS scores improved in all groups at 8 weeks, but statistical relevance was found in the low-dose BoNT-A group (with improvement maintained up to 6 months). Nevertheless, no serious side effects were detected in any group.[12]

The effect of 100 U BoNT-A (Botox; Allergan) on painful knee osteoarthritis was also evaluated in 46 subjects by Hsieh et al in a randomized controlled trial with a 6-month follow-up period. Authors found an average decrease in knee pain after a single-dose injection of 42.6% at 1 week posttreatment and 34.9% at 6 months posttreatment. The decrease in pain was more significant among patients with a higher baseline pain score measured with a VAS. Similar findings were observed for functional ability assessed using the Lequesne index and Western Ontario and McMaster Universities Arthritis Index (WOMAC).[13] BoNT efficacy has also been proven in pain associated with adhesive capsulitis.

A South Korean prospective controlled trial compared the effects of intra-articular BoNT-A (Dysport; 200 IU, n=15) with the steroid triamcinolone acetate in patients suffering from adhesive capsulitis of the shoulder. All patients were evaluated using a numeric rating scale of pain intensity and measurement of ROM at baseline and at 2, 4, and 8 weeks posttreatment. At week 8, both treatment groups showed significant improvements in pain, active shoulder abduction, and flexion, as well as the passive shoulder abduction and external rotation compared to baseline.[14] Pain control driven by BoNT-A has been also demonstrated in ankle osteoarthritis: authors compared the effects of intra-articular BoNT-A 100 U reconstituted in 2 mL normal saline and intra-articular hyaluronate (molecular weight 500–730 kDa) plus rehabilitation exercise in 75 patients.

The primary outcome measure was Ankle Osteoarthritis Scale score, and secondary outcome measures were American

Table 1 Key and reviewed studies on the employment of intra-articular botulinum toxin type A (BoNT-A)

Study	Design	Duration	Joint	Indication	Age, years	Patients (n)	BoNT-A injected	Main outcome measures	Main results
Mahowald et al[10]	Case series	12 months	Knee/ankle/shoulder	Chronic arthritis (OA, RA, psoriatic)	42–82	11 (15 joints)	25–100 U (onabotulinumtoxinA)	NRS, active ROM, TST	Maximum decrease in pain 55% (lower extremity) and 71% (shoulder)
Singh et al[11]	RCT	1 month	Shoulder	Shoulder OA	Mean 71	36 (43 joints)	100 U (unspecified)	VAS, SPADI, active ROM, SF-36, McGill Pain Questionnaire	61% of patients had 30% or ≥2 cm decrease in pain severity
Boon et al[12]	RCT, double blind, prospective	6 months	Knee	Knee OA	>40	60	100 or 200 U (unspecified)	VAS, WOMAC, SF-36, PGA, 40 m WT	VAS significantly improved in low-dose BoNT-A patients
Chou et al[16]	Prospective	6 months	Knee	Knee OA	>60	24 (38 joints)	100 U (onabotulinumtoxinA)	WOMAC	Effects clinically significant at 1 month after the first injection; WOMAC pain reduction at 3 months significant in stage 3 (Kellgren–Lawrence) patients, but not in stage 4
Joo et al[14]	RCT, prospective	8 months	Shoulder	Adhesive capsulitis	18–70	28	200 U (abobotulinumtoxinA)	NRS, active ROM	No significant differences between the 2 groups (BoNT-A and triamcinolone acetate)
Sun et al[15]	RCT, assessor-blinded	6 months	Ankle	Ankle OA		70	100 U (onabotulinumtoxinA)	AOS, AOFAS, VAS, SLST, TUG	No significant differences between the two groups (BoNT-A and hyaluronate)
Hsieh et al[13]	RCT, prospective	6 months	Knee	Knee OA	>45	46	100 U (onabotulinumtoxinA)	VAS, WOMAC, Lequesne index	Pain VAS scores in the BoNT-A group significantly decreased

Abbreviations: AOFAS, American Orthopedic Foot and Ankle Score; AOS, Ankle Osteoarthritis Scale; NRS, numeric rating scale; OA, osteoarthritis; PGA, patient global assessment; RA, rheumatoid arthritis; RCT, randomized clinical trial; ROM, range of motion; SF-36, 36-item short form health survey; SLST, single-leg stance test; SPADI, Shoulder Pain and Disability Index; TST, Timed Stands Test; TUG, timed up-and-go; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Arthritis Index; WT, walking test.

Orthopedic Foot and Ankle Society score, VAS pain score, single-leg stance test, timed up-and-go test, consumption of analgesics, and global patient satisfaction evaluated on a 0–7 Likert scale. Data showed improvements in pain, physical function, and balance, but no differences in effectiveness between the two interventions were found. These effects were rapid at 2 weeks and could last for at least 6 months.[15]

In an open-label study in 2010, 24 patients (38 knees) stage 3/4 knee osteoarthritis were included to receive two intra-articular injections of 100 U BoNT-A reconstituted with 4 mL normal saline at an interval of 3 months. Pain was assessed with the WOMAC index. Pain and stiffness improved clinically; however, the effect of BoNT-A achieved statistical significance only for the pain subscale in stage 3 osteoarthritis. After 3 months, only the subgroup with stage 3 disease showed a significant effect on WOMAC pain reduction. This subscore was still significantly diminished versus baseline after 5 and 6 months.[16]

Case series summary

We evaluated and treated six subjects aged 37–68 years with unilateral shoulder pain experienced for at least 6 months, with previous failure with conventional/standard treatment or who could not tolerate adverse effects of medications. They all reported moderate–severe pain, indicated by a rating of 30–50 mm on the VAS at rest and 50–80 mm during active movement. For pain measurement, we used a 100 mm ruler with 10 mm intervals. No subjects had received steroid or viscosupplement injections in the shoulder or any type of physical therapy in the previous 2 months.

Subjects who had a history of surgery involving the shoulder, other established chronic shoulder disorders, including rheumatoid arthritis or any inflammatory arthropathy, or who were pregnant were not treated. Shoulder radiographs taken within 6 months were obtained. An expert physician diagnosed concentric glenohumeral osteoarthritis in all patients. Patients were clinically assessed for the integrity and function of the rotator cuff, and when required a magnetic resonance imaging scan was performed to exclude rotator cuff tears.

The potential risks of intra-articular injection were explained before the procedure: all participants provided written informed consent for their data and any accompanying images to be included in this case series. This study and the treatment were approved by the institutional review board of the General Affairs and Privacy-Protection Office of "Ospedali Riuniti", Foggia, with protocol number 59. IncobotulinumtoxinA (100 U Xeomin; Merz Pharmaceuticals GmbH, Frankfurt, Germany) was injected into the symptomatic glenohumeral joint. One vial of BoNT-A (100 U) was reconstituted with 2 mL normal saline. The shoulder joint was injected using the posterior approach by inserting the needle 1 cm distally to the posterior corner of the acromion and advancing the needle anteriorly until the needle entered the posterior capsule (Figure 1).

Patients were evaluated at baseline and 4 weeks after the initial treatment. Subjects were instructed to avoid analgesic/anti-inflammatory drugs for 2 weeks after the BoNT-A injection and to abstain from the execution of painful activities of daily living involving the affected shoulder. The primary objective was to determine whether intra-articular injections of BoNT-A provided significant reduction in shoulder pain measured with the VAS.

The pain VAS is a continuous scale comprises a horizontal or vertical line, usually 10 cm in length, anchored by two verbal descriptors, one for each symptom extreme. For pain intensity, the scale is most commonly anchored by "no pain" (score of 0) and "pain as bad as it could be" or "worst imaginable pain" (score of 100 on 100 mm scale).[17] Patients were asked to evaluate the pain both at rest and during active shoulder movements.

The secondary outcome measure was the Constant–Murley score, the most commonly used scoring system to

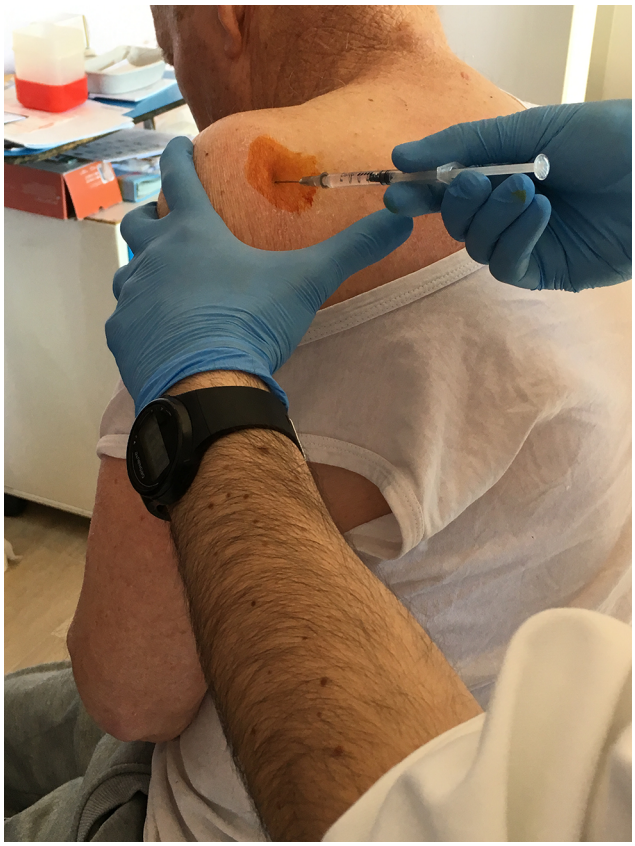

Figure 1 Glenohumeral injection technique with botulinum toxin A.

evaluate various disorders of the shoulder. It is a 100-point scoring system, in which 35 points are from patient self-report of pain and function and the remaining 65 points are allocated to objective assessment of ROM and strength. The self-report assessment includes a single item for pain (15 points) and four items for activities of daily living (work 4 points, recreation 4 points, sleep 2 points, and ability to work at various levels 10 points). The objective assessment includes ROM (forward elevation 10 points, external rotation 10 points, internal rotation 10 points, abduction 10 points) and power (scoring based on the number of pounds of pull the patient can resist in abduction, to a maximum of 25 points).[18] There was no follow-up loss or dropout. Demographic characteristics of the patients are shown in Table 2.

Discussion

In this article, evidence from existing studies and clinical observations about intra-articular BoNT-A supporting its antinociceptive action in humans is summarized. We also reported a case series focused on pain modulation in persistent shoulder pain in six subjects suffering from glenohumeral osteoarthritis. Change in pain severity, active function, and adverse events were evaluated for each patient after BoNT-A injection. All patients reported benefits in function measured with the Constant–Murley score and quality of life 30 days after BoNT-A injection. Findings from our case series aligned with all the studies reviewed.

There is no clinical "gold standard" defining shoulder pain; studies often rely on specific diagnosis. For preliminary recruitment, we considered pain in the shoulder and upper arm, at rest or caused or aggravated by movement.[19] Current standard care includes analgesics, nonsteroidal anti-inflammatory drugs, opioids, physical therapy, intra-articular steroids, hyaluronic acid, biomechanical adjustments, and activity modification to decrease pain. A significant proportion of patients fail conservative treatment and drugs are often associated with substantial side effects, especially in elderly patients, and thus when surgery may be contraindicated, the availability of a new therapeutic option would be desirable.

BoNT is actually the gold-standard therapy in the management of focal muscle hypertonia, blocking the release of acetylcholine at neuromuscular junctions in the muscle injected and resulting in a reduction in spasticity, dystonia, and related disorders.[20–22] The first description of BoNT-A used as an analgesic was conducted on patients with myofascial pain in a report by Cheshire et al.[23]

Many steps have followed this first attempt, and many in vitro, animal in vivo models, and human studies have demonstrated that BoNT-A shows high efficacy in the treatment of painful conditions, such as migraine, tension headaches, chronic tennis elbow, low-back pain, and piriformis syndrome.[24–27] These observations suggest an antinociceptive action for BoNT that may be independent of its paralyzing action. However, although the effect of BoNT-A on peripheral cholinergic synapses has been well characterized, the mechanism underlying the action on pain reduction is still unknown. Even less is known about articular pain relief. Joint structures contain Aδ, Aβ, and C fibers whose excitation threshold lowers in cases of injury and inflammation (peripheral sensitization).[28]

Chronic joint inflammation is also associated with hyperexcitability of spinal nociceptive neurons, referred to central sensitization.[29] A variety of mediators can sensitize joint nerves and nociceptors, including bradykinin, prostaglandin E_2, prostaglandin I_2, serotonin, substance P, and neuropeptide Y.[30] Persistent joint pain may lead to articular nociceptor sensitization and an increase in the release of neurotransmitters in the joint (neurogenic inflammation).[31]

Table 2 Demographic characteristics of patients and outcome measures at baseline (T0) and after 4 weeks (T1)

Age, years	Sex	Pain onset (months)	VAS at rest (mm)		VAS during active movement (mm)		Constant–Murley score			
			T0	T1	T0	T1	T0		T1	
							Pain + activity	Mobility + strength	Pain + activity	Mobility + strength
45	M	12	30	0	80	40	13	24	25	40
37	F	8	30	0	60	30	25	36	30	50
68	F	6	40	20	80	40	4	15	21	33
55	F	8	30	10	60	30	24	37	30	46
59	M	10	30	20	50	40	30	40	30	42
43	F	1	50	20	80	50	16	20	28	38

Abbreviations: F, female; M, male; VAS, visual analog scale.

BoNT-A has been found to inhibit substance P release from cultured embryonic dorsal-root ganglion neurons and to reduce stimulated (but not basal) release of calcitonin gene-related peptide from cultured trigeminal ganglion neurons. Based on these results, BoNT-A may inhibit the release of these neuropeptides in vivo, which may account for its beneficial effects on pain.[25,32,33] Human and nonhuman studies have shown cumulative effectiveness on pain reduction with no adverse events.[34,35]

Intra-articular BoNT-A injection has been also used for treatment of hemiplegic shoulder pain. Leaving out the antinociceptive effect due to spasticity reduction induced by intramuscular toxin injections at the level of the scapular girdle,[36,37] Castiglione et al found a 3±1.2-point decrease in VAS during passive abduction after 2 weeks and 2.3±1.1 points 8 weeks after a single intra-articular injection in five patients with hemiplegic shoulder pain.[38] The possibility of using BoNT-A therapy also for subjects without neurological disorders represents an effective treatment for shoulder pain due to musculoskeletal diseases.

Conclusion

Intra-articular BoNT-A is effective and minimally invasive, and no adverse events were observed. In light of this, although the number of subjects has been extremely small, our experience and the existing literature may point to botulinum intra-articular injection as a new treatment option for refractory shoulder pain due to osteoarthritis. More subjects, other dose ranges, different formulations, and interval studies of BoNT-A injections need to be examined further.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Steinfeld R, Valente RM, Stuart MJ. A commonsense approach to shoulder problems. *Mayo Clin Proc*. 1999;74:785–794.
2. Murphy RJ, Carr AJ. Shoulder pain. *BMJ Clin Evid*. 2010;2010:1107.
3. Andrews JR. Diagnosis and treatment of chronic painful shoulder: review of nonsurgical interventions. *Arthroscopy*. 2005;21:333–347.
4. Wissel J, Ward AB, Erztgaard P, et al. European consensus table on the use of botulinum toxin type A in adult spasticity. *J Rehabil Med*. 2009;41:13–25.
5. Smith HS, Audette J, Royal MA. Botulinum toxin in pain management of soft tissue syndromes. *Clin J Pain*. 2002;18:S147–S154.
6. Soares A, Andriolo RB, Atallah AN, da Silva EM. Botulinum toxin for myofascial pain syndromes in adults. *Cochrane Database Syst Rev*. 2014:CD007533.
7. Jankovic J, Schwartz K. Botulinum toxin injections for cervical dystonia. *Neurology*. 1990;40:277–280.
8. Göbel H, Heinze A, Heinze-Kuhn K, Jost WH. Evidence-based medicine: botulinum toxin A in migraine and tension-type headache. *J Neurol*. 2001;248:34–38.
9. Santamato A, Ranieri M, Panza F, et al. Botulinum toxin type A in the treatment of painful adductor muscle contracture after total hip arthroplasty. *Orthopedics*. 2009;32:43784.
10. Mahowald ML, Singh JA, Dykstra D. Long term effects of intra-articular botulinum toxin A for refractory joint pain. *Neurotox Res*. 2006;9:179–188.
11. Singh JA, Mahowald ML, Noorbaloochi S. Intra-articular botulinum toxin A for refractory shoulder pain: a randomized, double-blinded, placebo-controlled trial. *Transl Res*. 2009;153:205–216.
12. Boon AJ, Smith J, Dahm DL, et al. Efficacy of intra-articular botulinum toxin type A in painful knee osteoarthritis: a pilot study. *PM R*. 2010;2:268–276.
13. Hsieh LF, Wu CW, Chou CC, et al. Effects of botulinum toxin landmark-guided intra-articular injection in subjects with knee osteoarthritis. *PM R*. 2016;8:1127–1135.
14. Joo YJ, Yoon SJ, Kim CW, et al. A comparison of the short-term effects of a botulinum toxin type A and triamcinolone acetate injection on adhesive capsulitis of the shoulder. *Ann Rehabil Med*. 2013;37:208–214.
15. Sun SF, Hsu CW, Lin HS, Chou YJ, Chen JY, Wang JL. Efficacy of intraarticular botulinum toxin A and intraarticular hyaluronate plus rehabilitation exercise in patients with unilateral ankle osteoarthritis: a randomized controlled trial. *J Foot Ankle Res*. 2014;7:9.
16. Chou CL, Lee SH, Lu SY, Tsai KL, Ho CY, Lai HC. Therapeutic effects of intra-articular botulinum neurotoxin in advanced knee osteoarthritis. *J Chin Med Assoc*. 2010;73:573–580.
17. Price DD, Bush FM, Long S, Harkins SW. A comparison of pain measurement characteristics of mechanical visual analogue and simple numerical rating scales. *Pain*. 1994;56:217–226.
18. Constant CR, Murley AH. A clinical method of functional assessment of the shoulder. *Clin Orthop Relat Res*. 1987;160–164.
19. Buchbinder R, Green S, Youd JM. Corticosteroid injections for shoulder pain. *Cochrane Database Syst Rev*. 2003:CD004016.
20. Hallett M, Benecke R, Blitzer A, Comella CL. Treatment of focal dystonias with botulinum neurotoxin. *Toxicon*. 2009;54:628–633.
21. Esquenazi A. Botulinum neurotoxin in muscle overactivity. *J Head Trauma Rehabil*. 2005;20:563–567.
22. Santamato A. Safety and efficacy of incobotulinumtoxin A as a potential treatment for poststroke spasticity. *Neuropsychiatr Dis Treat*. 2016;12:251–263.
23. Cheshire WP, Abashian SW, Mann JD. Botulinum toxin in the treatment of myofascial pain syndrome. *Pain*. 1994 59:65–69.
24. Hayton MJ, Santini AJ, Hughes PJ, Frostick SP, Trail IA, Stanley JK. Botulinum toxin injection in the treatment of tennis elbow: a double-blind, randomized, controlled, pilot study. *J Bone Joint Surg Am*. 2005;87:503–507.
25. Aoki KR. Evidence for antinociceptive activity of botulinum toxin type A in pain management. *Headache*. 2003;43:S9–S15.
26. Santamato A, Micello MF, Valeno G, et al. Ultrasound-guided injection of botulinum toxin type A for piriformis muscle syndrome: a case report and review of the literature. *Toxins (Basel)*. 2015;7:3045–3056.
27. Jabbari, B. Evidence based medicine in the use of botulinum toxin for back pain. *J Neural Transm*. 2008;115:637–40.
28. Schaible HG, Richter F, Ebersberger A, et al. Joint pain. *Exp Brain Res*. 2009;196:153–162.
29. Neugebauer V, Galhardo V, Maione S, Mackey SC. Forebrain pain mechanisms. *Brain Res Rev*. 2009;60:226–242.
30. Schaible H, Schmelz M, Tegeder I. Pathophysiology and treatment of pain in joint disease. *Adv Drug Deliv Rev*. 2006;58:323–342.
31. Millan MJ. The induction of pain: an integrative review. *Prog Neurobiol*. 1999;57:1–164.
32. Arezzo JC. Possible mechanisms for the effects of botulinum toxin on pain. *Clin J Pain*. 2002;18:S125–S132.
33. Welch MJ, Purkiss JR, Foster KA. Sensitivity of embryonic rat dorsal root ganglia neurons to *Clostridium botulinum* neurotoxins. *Toxicon*. 2000;38:245–258.
34. Jabbari B. Botulinum neurotoxins in the treatment of refractory pain. *Nat Clin Pract Neurol*. 2008;4:676–685.

35. Anderson S, Krug H, Dorman C, McGarraugh P, Frizelle S, Mahowald M. Analgesic effects of intra-articular botulinum toxin type B in a murine model of chronic degenerative knee arthritis pain. *J Pain Res*. 2010;3:161–168.
36. Choi JG, Shin JH, Kim BR. Botulinum toxin A injection into the subscapularis muscle to treat intractable hemiplegic shoulder pain. *Ann Rehabil Med*. 2016;40:592–599.
37. Lim JY, Koh JH, Paik NJ. Intramuscular botulinum toxin-A reduces hemiplegic shoulder pain: a randomized, double-blind, comparative study versus intraarticular triamcinolone acetonide. *Stroke*. 2008;39:126–131.
38. Castiglione A, Bagnato S, Boccagni C, Romano MC, Galardi G. Efficacy of intra-articular injection of botulinum toxin type A in refractory hemiplegic shoulder pain. *Arch Phys Med Rehabil*. 2011;92:1034–1037.