

Treatment of Chronic Low Back Pain With Successive Injections of Botulinum Toxin A Over 6 Months

A Prospective Trial of 60 Patients

John P. Ney, MD,* Marc Difazio, MD,* Afsoun Sichani, BA,† William Monacci, MD,*
Leslie Foster, DO,* and Bahman Jabbari, MD‡

Objectives: The aim of this study was to evaluate the effects of two successive neurotoxin treatments for chronic low back pain using multiple pain rating scales in an open-label, prospective study.

Methods: Adult patients with chronic low back pain received multiple paraspinal muscle injections with a maximum dosing of 500 units of botulinum A toxin per session. Those with a beneficial clinical response received a second treatment at 4 months. Pain was assessed by visual analog scale (VAS), modified low back pain questionnaire (OLBPQ), and a clinical low back pain questionnaire (CLBPQ) at baseline, 3 weeks, 2 months, 4 months, and 6 months after the first treatment.

Results: Eighteen women and 42 men, ages 21 to 79 years (mean 46.6 years), with low back pain of a mean duration of 9.1 years were included. Significant improvement in back and radicular pain occurred at 3 weeks in 60% and at 2 months in 58% of the cohort. Beneficial clinical response to the first injection predicted response to reinjection in 94%. A significant minority of patients had a sustained beneficial effect from the first injection at 4 (16.6%) and 6 months (8.3%). Two patients had a transient flulike reaction after the initial treatment.

Conclusions: Botulinum toxin A improves refractory chronic low back pain with a low incidence of side effects. The beneficial clinical response is sustained with a second treatment.

Key Words: botulinum toxin A, Botox, back pain, radicular pain
(*Clin J Pain* 2006;22:363–369)

Received for publication October 10, 2004; revised May 1, 2005; accepted June 4, 2005.

From the *Department of Neurology, Uniformed Services University of the Health Sciences, Bethesda, MD, and Walter Reed Army Medical Center, Washington DC; †University of Maryland, College Park, MD; and ‡Department of Neurology, Yale University, New Haven, CT.

Supported by a grant from Allergan, Inc, Irvine, CA.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Reprints: John P. Ney, MD, Walter Reed Army Medical Center, Department of Neurology, 6900 Georgia Ave., NW, Bldg #2, Washington, DC 20307 (e-mail: John.Ney@na.amedd.army.mil or jney_pubs@yahoo.com).

Copyright © 2006 by Lippincott Williams & Wilkins

Back pain is one of the most costly health conditions in Western nations.¹ In the United States alone, low back pain claims total \$8.8 billion annually and represent one quarter of all worker's compensation expenses in the country.² Low back pain is the second most common reason for doctor's appointments.³ Chronic low back pain has been attributed to various causes, including disc herniation,⁴ degenerative spine changes,⁵ spinal subluxation,⁶ muscle spasm,⁷ and facet joint inflammation.⁸ Muscle relaxants, nonsteroidal anti-inflammatory drugs (NSAIDs), antidepressants, and opioids are the most used noninvasive treatments. Measures such as physical therapy, TENS, chiropractic, and alternative medicine are practiced frequently and add to the treatment cost.

The treatments currently available for low back pain are not devoid of problems. The effects of muscle relaxants are often ephemeral and fail to reach statistical significance in clinical trials.⁹ Opioid medications expose the patient to the dangers and stigma of addiction,¹⁰ as well as fatigue and cognitive impairment.¹¹ When taken at high doses, virtually all systemic medications used for amelioration of low back pain produce unpleasant or possibly dangerous side effects.^{12,13} Steroid injections,¹⁴ facet blocks,¹⁵ and more invasive treatments such as laminectomy¹⁶ often produce transient results, with the potential for serious medical complications. The failure rate for lumbar surgery ranges from 10% to 40%.¹⁷ With the wide variety of causes for low back pain, uniform treatment approaches have failed to show a consistent response, leaving patients dissatisfied and frustrated.

Botulinum toxin A (Botox, Allergan Inc, Irvine, CA), a potent inhibitor of acetylcholine, has shown benefit in a number of painful medical conditions.^{18–24} A small, double-blind study showed that a single treatment was effective in patients with chronic low back pain.²⁵ We report the results of an open-label, prospective study evaluating the effect of repeated injection of botulinum toxin A in a larger cohort of patients with refractory chronic low back pain.

METHODS

Patients were enrolled in this prospective open-label protocol if they met the following inclusion criteria:

(1) chronic and stable low back pain of at least 6 months' duration, (2) ages 18 to 80 years old, (3) no acute pathology, to include infection, neoplasm, or fracture evident on lumbosacral MRI, (4) failure of medical or surgical treatments, (5) no current or planned pregnancy, (6) no ongoing litigation or worker's compensation claims, (7) no systemic inflammation, (8) no disorders of neuromuscular transmission, and (9) no known allergy or sensitivity to botulinum toxin A. Patients with prior lumbar surgery were allowed in the study. Patients were instructed not to escalate the dosing or frequency of analgesics and to avoid using new analgesics. They were also instructed to make no changes in their physical therapy regimen as prescribed by routine clinical practice. Females of childbearing age were screened for pregnancy with a urine pregnancy test. Patients were identified as having chronic low back pain by neurologists, neurosurgeons, and physical medicine physicians in clinical practice and referred to our study. All decisions on whether to include patient data in the analysis were carried out before trial entry.

The study was approved by the Walter Reed Army Medical Center Institutional Review Board (IRB). All patients signed an informed consent form before participation.

All patients were interviewed and examined at baseline by a neurologist. Subjects were assessed at baseline, then at 3 weeks, 2 months, 4 months, and 6 months after the first treatment. At each session, subjects completed a clinical low back pain questionnaire (CLBPQ) regarding the number of days in the previous 28 that they had significant low back pain.²⁶ Subjects rated their maximal and average pain for the preceding 28 days on a visual analog scale (VAS) using a 10-cm horizontal axis between a left end point of "no back pain" and a right end point of "worst pain ever." The distance was measured and pain was recorded on a 10-point scale.²⁷ Subjects also completed the Oswestry Low Back Pain Questionnaire (OLBPQ), which summarizes functional limitation in subsets, including overall pain, lifting, standing, and walking, with a scale total ranging from 0 (no limitation) to 49 (most disabled).²⁸

The patient's response to botulinum toxin A was considered beneficial and significant when improvement occurred in least two of the following ratings: (1) VAS (average) showed 50% or more decrease in pain intensity; (2) OBLPQ showed a two-grade or more improvement in the pain subset and one or more of the functional subsets; and (3) CLBPQ showed a 30% or more decrease in the number of pain days from baseline.

Botulinum toxin A, concentrated at 100 units/mL, was injected with a 1-cc tuberculin syringe through a 0.75- or 1.5-inch needle, depending on the degree of subject adiposity. Four or five injection sites per side from L2 to S1 were determined by the physician and patient based on deep finger pressure to locate trigger points or muscle spasm. Injections were done without electromyographic guidance due to the size of muscles involved, the additional expense and equipment costs, and the relative

ease of clinically determining painful or overactive sites of paravertebral muscles.²⁹ The dose per site was similar to prior studies²⁵ at 40 to 50 units, and the total dose per session did not exceed 500 units for bilateral pain (Foster et al²⁵ did not exceed 200 units total for unilateral pain only). Patients were instructed to report side effects at any time during the study.

Botulinum toxin injections were to occur at the time of entry into the study. The duration of effect was assumed to decline by 4 months.³⁰ A second set of injections would be given at 4 months if the patient had a significant beneficial response at 2 months. Patients with continued clinical benefit past 4 months would be allowed to defer reinjection. Follow-up was to occur at 3 weeks after the initial injection, then at 2-month intervals thereafter. Failure to respond at 3 weeks or 2 months warranted no further follow-up.

Statistical significance and relevant *P* values were calculated by comparison to baseline scores in the three rating scales using the Student two-tailed *t* test for significance on SPSS software, version 12.0 (SPSS Inc, Chicago, IL.).

RESULTS

All patients were adults. Of the 65 patients referred, 18 women and 42 men were enrolled. Mean age was 46.6 years (range 21–79) at time of entry. Five patients failed to meet the inclusion criteria. A variety of clinical and demographic factors were analyzed, including age, sex, pain intensity, duration, laterality, medications, presence of radicular pain, history of back surgery, and MRI findings (Table 1). Thirty-seven patients (61.6%) had concurrent radicular pain radiating to one leg. In 20 patients radicular pain was the most disabling symptom. Forty-seven patients (78.3%) took one or more medications for pain and 17 patients (28.3%) took narcotic analgesics (typically oral preparations containing oxycodone or meperidine). Eleven (18.3%) patients had undergone previous back surgery, and four had more than one back surgery. MRI reports were abnormal but without acute pathology such as infection, fracture, or neoplasm in all but two patients. MRI abnormalities depicting chronic changes commonly consisted of single- or multiple-level lumbar/lumbosacral disc protrusions, canal narrowing, degenerative changes, or a combination of these structural abnormalities.

At baseline, the mean average VAS score (over the prior 28 days) was 5.3 and the mean maximum pain VAS score was 8.58 (out of 10, highest pain). The mean OLBPQ score was 17.2 (0 being no disability and 49 being worst). The mean number of days with significant low back pain identified on the CLBPQ was 23.8 (out of the past 28 days).

Sixty patients were injected at the time of entry. Three weeks after injection, 60% of the patients had a beneficial response. Two months after injection, 58% of the initial cohort had a beneficial response. Four months after injection, 16.6% of the patients reported continued

TABLE 1. Demographic and Clinical Data of 60 Patients

Age (mean)	46.6 years (range 21 to 79)
Male/Female	42/18
Duration of pain (mean)	9.1 years (range 6 months to 50 years)
Unilateral pain	11 (18.3%)
Bilateral pain	49 (81.7%)
Taking pain medication	47 (78.3%)
Taking opioids	17 (28.3%)
Previous back surgery	14 (23.3%)
Neurologic deficits	22 (36.7%)
History of back trauma	26 (43.3%)
VAS baseline maximum pain score (mean)	8.58 (range 5.7–10)
OLBPQ baseline functionality score (mean)	17.2 (0-no disability) (range 4–30)
CLBPQ baseline (number of pain days in past 28) (mean)	23.8 days (range 3–28 days)
Root pain	37 (61.6%)

VAS, visual analog scale; OLBPQ, Oswestry low back pain questionnaire; CLBPQ, clinical low back pain questionnaire.

benefit and the decision was made not to retreat at that time. Six months after the initial injection, five patients (8.3% of the initial cohort) reported sustained effect and were not reinjected (Table 2). However, the majority of those who experienced a beneficial response at 2 months after injection (22/35) reported that benefit had waned by 4 months. These patients were reinjected at 4 months. Patients with no beneficial response at 3 weeks and 2 months were not reinjected at 4 months.

After reinjection, 18 of 19 patients (3 of the 22 injected were lost to follow-up) followed at 6 months (2 months after reinjection) reported a beneficial response (see Table 2). A binomial distribution comparing this last result with a predicted success rate of 60% (from Foster et al's²⁵ 2-month success rate) yielded $P < 0.005$. A total of 10 patients were lost to follow-up, largely a reflection of increased mobilizations in the active-duty military contingent of our cohort.

Twenty-two of 37 initial responders had radicular pain. Paraspinal treatment with botulinum toxin A resulted in a significant improvement in radicular pain in 15 of these 22 patients (68%). In 9 of 15 responders (60%), the disabling radicular pain totally ceased over the period of observation (4 to 6 months).

Responders and nonresponders were compared in relation to a number of demographic and clinical factors (Table 3). There were no significant differences between

the two groups with respect to age, sex, pain intensity, duration, laterality, history of back trauma or surgery, presence of root pain, and presence of neurologic deficits. In general, the group taking opioid medications at entry did not respond as well as those not taking opioid analgesics ($P = 0.041$). However, several patients in group taking opioids analgesics had a significant response. Three of these responders had no need to take opioid medications during the first 3 months after botulinum toxin A treatment. Half of the responders who were taking nonnarcotic medications reported a reduction in their nonnarcotic "pill" intake by 50 to 90%.

Mean VAS, OLBPQ, and CLBPQ values at baseline, 3 weeks, 2 months, and 6 months (Fig. 1) showed notable improvement after botulinum toxin A treatment. Two patients (3.3%) reported a side effect consisting of a mild, flu-like reaction lasting 3 to 5 days. No patients reported muscle weakness.

DISCUSSION

Botulinum toxin A as a therapeutic intervention for pain evolved from the earliest trials in the management of cervical dystonia (spasmodic torticollis), a muscle overaction syndrome with pain present in up to 80% of those affected. In several double-blind, placebo-controlled

TABLE 2. Responders Versus Nonresponders and Response to Reinjection

	Number of Responders and Nonresponders to First Injection				Response to Reinjection at 4 Months After Initial Injection
	3 Weeks (n = 60)	2 Months (n = 37)	4 Months (n = 35)	6 Months (n = 10)	Recorded 2 Months After Reinjection (6 Months From Initial Injection) (n = 22)
Response	37	35	10	5	18
No response	19	2	22	5	1
Lost	4	0	3	0	3

Those with clinical response at each interval are the total number of patients followed up at the next time interval. Those reinjected had a favorable response to initial injection at 2 months but were nonresponders at 4 months.

TABLE 3. Responders Versus Nonresponders at 3 Weeks: Demographic and Clinical Factors

	Responders	Nonresponders
Total #	37 (60%)	23 (40%)
Age (mean)	44.6 years (range 22–76)	49.9 years (range 21–76)
Male/Female	26/11	16/7
Intensity	7.9 (range 3.5–10)	7.2 (range 5–10)
Duration of pain	9.6 years (range 6 months to 30 yrs.)	8.4 years (range 7 months to 50 yrs.)
Bilateral pain	32 (86.5%)	17 (73.9%)
Unilateral pain	5 (13.5%)	6 (26.1%)
On medication	29 (78.3%)	17 (73.9%)
On opioids (<i>P</i> = 0.041)	7 (18.9%)	10 (43.5%)
Previous surgery	10 (27.0%)	4 (17.4%)
Back trauma	17 (46.0%)	9 (39.1%)
Radicular pain	22 (59.5%)	15 (65.2%)
Neurologic deficits	13 (35.1%)	9 (39.1%)

trials, greater than 75% of treated patients with torticollis had significant pain relief, in addition to improved postural control.^{18–20} Subsequent investigators looked at the role of neurotoxins in myofascial pain syndrome (MPS), a condition characterized by trigger points of firm nodules or taut bands within muscle. Early studies of botulinum toxin A injected directly into trigger points for MPS produced mixed effects,²¹ but more recent trials reported 72% to 80% improvement of symptoms after injection.^{22–24}

Although these studies of MPS showed a significant response to botulinum toxin A in some patients with neck and low back pain, dedicated investigations of botulinum toxin A effect on low back pain are scarce. Review of the literature yielded two randomized and one retrospective study of the use of botulinum toxin A and one open-label

prospective study of botulinum toxin B. No long-term or large cohort studies were found.³¹

Foster et al²⁵ conducted a randomized, placebo-controlled, double-blind study of botulinum toxin A versus saline injection in 31 patients with unilateral or predominantly unilateral low back pain. Patients were evaluated by VAS and OLBPQ at baseline, 3 weeks, and 2 months. After injection into paravertebral muscles, 73% of subjects at 3 weeks and 60% at 3 weeks and 2 months had a significant response. Limitations of this study were the small size of cohort (15 patients received botulinum toxin A) and the short duration of observation. The authors reported no significant side effects.

Subin et al³² reported the results of a smaller randomized trial in which 19 patients with low back pain were seen in a pain management clinic and initially rated

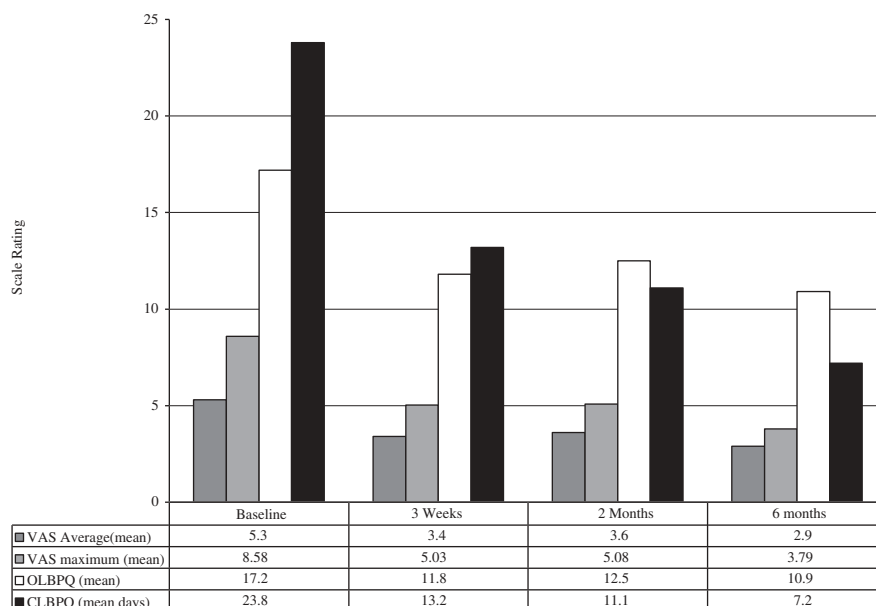


FIGURE 1. Comparison of mean baseline and subsequent post-treatment scores of pain intensity. VAS, visual analog scale; OLBPQ, Oswestry low back pain questionnaire; CLBPQ, clinical low back pain questionnaire.

P value is significant for all comparisons with baseline (*P* < 0.005).

using VAS, OLBPQ, Roland-Morris Disability Score, and McGill Pain Score. Nine of these patients were injected and the remainder were used as controls. Follow-up at 1 and 6 months showed improvement in the McGill Score in seven of the nine treated patients and five of the nine patients on the Oswestry and Roland-Morris scores. No controls showed improvement. The degree and time course of improvement were not stated, and additional follow-up or repeated injection data was not given. The authors denied any side effects to treatment.

Edwards and Dreyer³³ reviewed their experience with botulinum toxin A treatment in 17 patients whose pain failed to respond to back surgery and who were left with chronic disabling back pain. In this retrospective review, comparison of pre- and post-treatment VAS and McGill Pain results showed significant improvements in both rating scales. No patient developed muscle weakness as the result of treatment.

Opida³⁴ conducted an open-label, prospective study of botulinum toxin B (Myobloc, Elan Pharmaceuticals) in 35 patients with nonradiating chronic low back pain. Pain was rated on a 10-point VAS at time of entry and at 3 and 12 weeks after injection. Botulinum toxin B was administered at 10,000 units, divided equally among four paravertebral levels (L2-3, L3-4, L4-5, L5-S1). Two thirds of subjects reported diminution of pain on the VAS by 3.6 points at 4 weeks ($P < 0.001$), and 4.8 points at 12 weeks ($P < 0.001$) after injection. No follow-up or reinjection data were provided past 3 months.

Our report supports the benefit and safety of paraspinal administration of botulinum toxin A for low back pain that was shown in the aforementioned studies. It also shows three new findings. First, initial beneficial response predicts a beneficial response to the second treatment ($P < 0.005$). Second, radicular pain improves concurrently with low back pain in the majority of responders (68%). Finally, in low back pain, the significant response may persist beyond the typical 3 to 4-month period in a sizeable number of responders (27% of responders at 4 months and 13% at 6 months). The cause of this long-duration response is not clear. It may relate to the nature of the disorder, the treatment technique, genetic factors, normalization of previously sensitized peripheral or central neurons, or direct effect of botulinum toxin A on muscle fibers.

The exact neurophysiology of botulinum toxin A in promoting pain relief remains a subject of investigation, but mechanisms of peripheral and central nervous system production of pain have been suggested.^{35,36} Botulinum toxin binds to presynaptic cholinergic nerve terminals, is internalized to nerve cytosol, and inhibits the formation of the SNARE protein complex essential for exocytosis of acetylcholine-carrying vesicles.^{37,38} This effect lasts for several months, with eventual return of function at the original synapse. The effect of the botulinum toxins at the neuromuscular junction has significant implications in the amelioration of muscle pain. Muscle pain may arise through the activation of thinly myelinated group 3 and nonmyelinated group 4 afferents (40% of which are

nociceptors)³⁶ concurrent with alpha-motor neuron overaction in abnormal contraction patterns, as seen in cramping and spasm.³⁹ By reducing the alpha-motor neuron release of acetylcholine, local factors acting as nociceptive transmitters, such as substance P and bradykinin,⁴⁰ are diminished in turn. More central mechanisms may play a part in chronic pain syndromes, owing to the increased sensitivity of wide dynamic range (WDR) spinal neurons.⁴¹ Under pathologic chronic conditions, nonpainful stimuli may be perceived as painful due to a failure in stimulus discrimination of the WDR neurons. Nociception is exaggerated as a wider range of peripheral inputs are seen as painful, contributing to the chronic pain state.⁴² Botulinum toxins may lower the available inputs to the WDR neurons, attenuating pain perception. One such nonnociceptive input comes from muscle spindles, which discharge less after being exposed to botulinum toxin A.⁴³ Regional blood flow patterns may be altered by the inhibition of postganglionic cholinergic fibers within muscle blood vessels, reducing ischemia and diminishing sensitization of muscle nociception by local factors. These effects combine to reduce central perception of pain through neuroplastic mechanisms in the central nervous system.^{44,45}

Botulinum toxin A may also modulate pain by interrupting glutamatergic transmission. Glutamate may be involved in the induction or maintenance of local pain, as glutamate accumulation has been seen at the site of local nociceptive pathology such as injured tendons and discs.^{46,47} Cui et al⁴⁸ showed the benefit of botulinum toxin A for pain in animals treated with formalin to induce local inflammation and pain. Pretreatment with botulinum neurotoxin resulted in a reduction in the local accumulation of glutamate and dose-dependent attenuation of pain-related behaviors. This implies inhibition of neurotransmission by botulinum toxins independent of neuromuscular blockade.

Our study was limited because it was not randomized or blinded. The extent of patient and physician bias is unclear. Patients could have a larger or smaller estimate of the effect of the medication, based on preconceived expectations. Although the patients were responsible for gauging the effect of the medication, encounters with physicians administering successive injections of botulinum toxin A may introduce additional bias. The "placebo effect" was not assessed. Due to the lack of randomization, the results can only be suggestive of benefit rather than scientifically conclusive. Randomized trials are needed for conclusive proof of benefit. Sample error is potentially a problem, as patients were a convenience sample referred from specialists in the treatment of low back pain, suggesting a cohort less responsive to conventional interventions available from a primary care physician. This may lead to an underestimate of the study treatment benefit, as many of the study subjects may have pain that is "harder to treat" than the general population with chronic low back pain. Lastly, a number of study patients dropped out from the first to second treatment,

due in large part to military mobilizations. With these dropouts included in a "last result carried forward" analysis, the response rate among initial responders to a second injection at 6 months would have increased to 96% ($P < 0.005$). Alternately, if the dropouts from months 2 to 6 were included as nonresponders, the response rate would have been only 72% ($P = 0.08$). This would reduce the predictive power of the initial response to botulinum toxin A for success of subsequent injections.

The results of our study are encouraging. Over half of the study patients with chronic low back pain responded to botulinum toxin A treatment. Initial response in our study was predictive of response with a second treatment. Paraspinal treatment of botulinum toxin A ameliorated the lumbar radicular pain of a sizeable number of patients. Side effects of botulinum toxin A treatment of low back pain were uncommon and mild and did not cause appreciable weakness or gait instability in the doses administered.

ACKNOWLEDGMENT

The authors acknowledge the help of Mrs. Elena Pesin as the coordinator of this study.

REFERENCES

- Goetzel RZ, Hawkins K, Ozminowski RJ, et al. The health and productivity cost burden of the "top 10" physical and mental health conditions affecting six large US employers in 1999. *J Occup Environ Med.* 2003;45:5–14.
- Rosenbaum R, Franklin G, Clemmons D, et al. Low back pain. *Continuum.* 2001;44–63.
- Miller CE. Arthritis and the role of the physician in nonmalignant pain and disability. *J Health Soc Policy.* 2002;16:33–42.
- Lutz GK, Butzlaff M, Schultz-Venrath U. Looking back on back pain: trial and error of diagnoses in the 20th century. *Spine.* 2003;28:1899–1905.
- Bono CM. Low-back pain in athletes. *J Bone Joint Surg [Am].* 2004;86:382–396.
- Benoist M. Natural history of the aging spine. *Eur Spine J.* 2003;12:S86–S89.
- Borenstein DG. Chronic low back pain. *Rheum Dis Clin North Am.* 1996;3:439–456.
- Dreyfuss PH, Dreyer SJ. Lumbar zygapophysial (facet) joint injections. *Spine J.* 2003;50S–59S.
- Cole A. Drug therapy in acute and chronic low back pain in primary care. In: Bartley R, Coffey P, ed. *Management of Low Back Pain in Primary Care.* Oxford, England: Butterworth-Heinemann; 2001:147–152.
- Reid MC, Engles-Horton LL, Weber MB, et al. Use of opioid medications for chronic noncancer pain syndromes in primary care. *J Gen Intern Med.* 2002;17:173–179.
- Burgess FW. Opioid therapy for chronic painful conditions. *Med Health R I.* 2001;10:323–326.
- van Tulder MW, Scholten RJ, Koes BW, et al. Nonsteroidal anti-inflammatory drugs for low back pain: a systematic review within the framework of the Cochrane Collaboration Back Review Group. *Spine.* 2000;25:2501–2513.
- van Tulder MW, Touray T, Furlan AD, et al. Muscle relaxants for non-specific low back pain. *Cochrane Database Syst Rev.* 2003;2:CD004252.
- Koes BW, Scholten RJ, Mens JM, et al. Efficacy of epidural steroid injections for low-back pain and sciatica: a systematic review of randomized clinical trials. *Pain.* 1995;63:279–288.
- van Kleef M, Barendse GA, Kessels A, et al. Randomized trial of radiofrequency lumbar facet denervation for chronic low back pain. *Spine.* 1999;24:1937–1942.
- Gibson JN, Grant IC, Waddell G. The Cochrane review of surgery for lumbar disc prolapse and degenerative lumbar spondylosis. *Spine.* 1999;24:1820–1832.
- Gundry CR, Heithoff KB. Lumbar spine imaging. In: Kirkaldy-Willis WH, Bernard T, eds. *Managing Low Back Pain.* Philadelphia: Churchill Livingstone; 1999:176–205.
- Tsui JK, Eisen A, Stoessl AJ, et al. Double-blind study of botulinum toxin in spasmodic torticollis. *Lancet.* 1986;2:245–247.
- Jankovic J, Schwartz K, Donovan DT. Botulinum toxin injections for cervical dystonia. *Neurology.* 1990;40:277–280.
- Wheeler AH, Goolkasian P, Gretz SS. A randomized, double-blind, prospective pilot study of botulinum toxin injection for refractory unilateral cervicothoracic, paraspinal, myofascial pain syndrome. *Spine.* 1998;23:1662–1667.
- Cheshire WP, Abashjan SW, Mann JD. Botulinum toxin in the treatment of myofascial pain syndrome. *Pain.* 1994;59:65–69.
- Wheeler AH, Goolkasian P. Open label assessment of botulinum toxin A for pain treatment in a private outpatient setting. *J Musculoskeletal Pain.* 2001;67–82.
- Lang AM. A pilot study of botulinum toxin type A (BOTOX®) administered using a novel injection technique, for the treatment of myofascial pain. *Am J Pain Manage.* 2000;10:108–112.
- De Andreas J, Cerda-Olmedo G, Valia JC, et al. Use of botulinum toxin in treatment of chronic myofascial pain. *Clin J Pain.* 2003;19:269–275.
- Foster L, Clapp L, Erickson M, et al. Botulinum toxin A and chronic low back pain. *Neurology.* 2001;56:1290–1293.
- van Poppel MN, Koes BW, van der Ploeg T, et al. Lumbar supports and education for the prevention of low back pain in industry: a randomized controlled trial. *JAMA.* 1998;279:1789–1794.
- Price DD, Bush FM, Long S, et al. A comparison of pain measurement characteristics of mechanical visual analogue and simple numerical rating scales. *Pain.* 1994;56:217–226.
- Fairbanks JCT, Couper J, Davies JB, et al. The Oswestry Low Back Pain Disability Questionnaire. *Physiotherapy.* 1980;66:271–273.
- Jankovic J. Needle EMG guidance is rarely required. *Muscle Nerve.* 2001;24:1568–1570.
- Tsui JKC. Botulinum toxin as therapeutic agent. *Pharmacol Ther.* 1996;72:13–24.
- Jabbari B, Ney JP. Treatment of low back pain with botulinum neurotoxins. *Pain Pract.* 2004;4:S47–S53.
- Subin B, Saleemi S, Morgan GA, et al. Treatment of chronic low back pain by local injection of botulinum toxin A. The Internet Journal of Anesthesiology. 2003. v6. Available at <http://www.uam.es/departamentos/medicina/anesnet/journals>. Accessed April 6, 2005.
- Edwards K, Dreyer M. Botulinum type A for failed back syndrome. *J Pain.* 2004;5:S63.
- Opida CL. Open-label study of Myobloc (botulinum toxin B) in the treatment of patients with chronic low back pain. *Naunyn-Schmiedeberg Arch Pharmacol.* 2002;365:PR33.
- Lang AM. Botulinum toxin type A therapy in chronic pain disorders. *Arch Phys Med Rehabil.* 2003;84:S69–S73.
- Borodic GE, Acquadro M, Johnson EA. Botulinum toxin therapy for pain and inflammatory disorders: mechanisms and therapeutic effects. *Expert Opin Investig Drugs.* 2001;8:1531–1544.
- Setler P. Therapeutic use of botulinum toxins: background and history. *Clin J Pain.* 2002;18:S119–S124.
- Meunier FA, Schiavo G, Molgo J. Botulinum neurotoxins: from paralysis to recovery of functional neuromuscular transmission. *J Physiol.* 2002;96:105–113.
- Schomburg ED, Stephens H, Klaus-Dieter K. Contribution of group III and IV afferents to multisensorial spinal motor control in cats. *Neurosci Res.* 1999;33:95–206.

40. Arezzo JC. Possible mechanisms for the effects of botulinum toxin on pain. *Clin J Pain*. 2002;18:S125–S129.
41. Graven-Nielsen T, Mense S. The peripheral apparatus of muscle pain; evidence from animal and human studies. *Clin J Pain*. 2001;17:2–10.
42. Craig AD. Pain mechanisms: labeled lines versus convergence in central processing. *Annu Rev Neurosci*. 2003;26:1–30.
43. Roberts WJ. A hypothesis on the physiological basis for causalgia and related pains. *Pain*. 1986;3:297–311.
44. Fillipi GM, Errico P, Santarelli R, et al. Botulinum A toxin effects on rat jaw muscle spindles. *Acta Otolaryngol*. 1993;113:4000–4004.
45. Mannion RJ, Woolf C. Pain mechanisms and management: a central perspective. *Clin J Pain*. 2000;16:S144–S156.
46. Harrington JF, Messier AA, Bereiter D, et al. Herniated lumbar disc material as a source of free glutamate available to affect signals through the dorsal root ganglion. *Spine*. 2000;25:929–936.
47. Alfredson H, Lorentzon R. Chronic tendon pain: no signs of chemical inflammation but high concentrations of the neurotransmitter glutamate. Implications for treatment? *Curr Drug Targets*. 2002;3:43–54.
48. Cui M, Khanijou S, Rubino J, et al. Subcutaneous administration of botulinum toxin A reduces formalin-induced pain. *Pain*. 2004;107:125–133.