

# Temporal Relationship of Muscle Weakness and Pain Reduction in Subjects Treated With Botulinum Toxin A

Brian Freund and Marvin Schwartz

**Abstract:** Botulinum toxin A has demonstrated efficacy in relieving pain in spastic and nonspastic muscle conditions. This analgesic property has generally been attributed to muscular relaxation. This study demonstrates initial muscular relaxation and concomitant pain relief in a masticatory muscle model. However, as muscle power returns to normal, pain relief is still very evident. This result suggests that the analgesic effect attributed to botulinum toxin is more complex than simple muscular relaxation.

© 2003 by the American Pain Society

**Key words:** Pain, muscle contraction, botulinum toxin-A.

During the past decade the use of botulinum toxin A (BTX-A) has become an integral part of spasticity management. It has proved useful in relaxing the musculature and in relieving the accompanying pain. Several reports, however, noted that the pain relief obtained in spastic conditions appeared to be disproportionately profound with respect to the degree of relaxation obtained in the involved muscles.<sup>52</sup> Therefore, muscle relaxation alone may not explain the relief of pain experienced by individuals treated with BTX-A. This study examines the time course of muscle relaxation and pain relief with the masticatory system as a model.

## Methods

This prospective open label study enrolled 35 subjects from general practice. Subjects reviewed the protocol and signed an informed consent approved by our local ethics committee. Each enrolled subject was diagnosed with muscle-centered temporomandibular disorder (TMD). This form of TMD was characterized by pain primarily located in one or both masseter muscles. The location of this pain was defined through subject reporting during tooth clenching exercises and confirmed through digital palpation of the masseters. All subjects had a history of bruxism or clenching and experienced some pain relief in the past with centrally acting oral muscle relaxant medications such as benzodiazepines, antihistamine derivatives, tricyclic derivatives, or  $\gamma$ -aminobutyric acid derivatives. Subjects were otherwise healthy and free from coexisting chronic pain conditions.

BTX-A in the form of BOTOX (Allergan Inc, Irvine, CA) was reconstituted with 2.0 mL of unpreserved saline per

100-unit vial, yielding a 5 units/0.1 mL solution. Preparation and handling were carried out as directed in the product insert. Injections were limited to the masseter and temporalis muscles bilaterally regardless of whether the TMD was one-sided or bilateral. The masseters received 50 units each of BTX-A in 0.2-mL aliquots divided over 5 sites. All injections were percutaneous and intramuscular as verified by electromyographic (EMG) guidance. Similarly the temporalis muscles were injected with a dose of 25 units in 0.1-mL aliquots divided over 5 sites. Injection sites corresponded to areas of greater muscle mass by palpation and greater activity established via EMG, but not necessarily corresponding to trigger points. Because it has been shown that EMG-based heterogeneity exists in both temporalis and masseter muscles, which is task dependent,<sup>4</sup> clenched muscle was used to determine areas of higher EMG activity. This injection protocol has proved to be effective for TMD in 2 previous studies.<sup>18,19</sup>

Subjects completed a visual analogue scale (VAS) for facial pain as well as having maximum voluntary bite force recorded at their first appointment, before injections. Only 1 set of injections was administered to subjects during the study ( $T_0$ ). Pain and bite force were recorded at 2-week intervals for a total of 5 recordings ( $T_0$ ,  $T_2$ ,  $T_4$ ,  $T_6$ , and  $T_8$ ). Subjective pain scores were based on a VAS composed of a 10-cm horizontal line with a 0 at the left end and a 10 at the right end. Subjects were asked to place an X on the line corresponding to a pain score in which 0 is no pain and 10 is "the worst facial/jaw pain you have had."

The bite force recordings were obtained by using a custom-fabricated bite force meter. It consisted of a piezo pressure transducer that was placed between the front teeth. Subjects were instructed to bite down as hard as they could for as long as they could. The pressure generated between the 2 front upper and lower teeth was converted to an electrical signal, which was amplified and reported by the hardware in avoirdupois pounds. (Some studies report bite pressure in newtons

Received November 16, 2001; Revised August 21, 2002; Re-revised October 14, 2002; Accepted October 14, 2002.

From the Faculty of Dentistry, University of Toronto and The Crown Institute, Toronto, Canada.

Address reprint requests to B. Freund, DDS, MD, 944 Merritton Road, Suite 100, Pickering, Ontario L1V 1B1, Canada. E-mail: brian.freund@utoronto.ca

© 2003 by the American Pain Society

1526-5900/2003 \$30.00 + 0

doi:10.1054/jpai.2003.435

(N), in which 4.45 N = 1 lb.) The study coordinator placed the transducer between the teeth in an indexed position on each occasion and initiated the recording. A minimum of 5 seconds of consistent maximum bite pressure was considered to be a satisfactory recording; this satisfactory interval was determined by the hardware. The bite force data were then uploaded to a computer for analysis by custom-written software. Further VAS and bite force measurements were completed during follow-up appointments in the clinic. Attempts were made to have consistent appointments for individual subjects to minimize the influence of daily routine. Therefore, appointments were scheduled on the same day of the week as well as the same time of day for each follow-up visit. Subjects were also questioned by the study coordinator about changes in medical history, changes in medication usage, changes in chewing function, as well as for occurrence of adverse events. Adverse events occurring between follow-ups were reported by subjects by phone and documented by the study coordinator. Any event considered as serious by the investigator was followed up in person.

Neither the bite force meter nor the VAS has been validated for use in TMD; however, they have been used in a previous study.<sup>19</sup>

Correlation analysis was carried out between demographic data including age, sex, weight, length of time of condition, education, and income level as well as for pain and bite force measurements (Pearson correlation coefficients) at each time period. Significant changes in the means (paired *t* test) of each outcome measure between every time point were also tested.

## Results

All 35 subjects completed the study. Twenty-six subjects were women; the mean age of the entire group was 29 years (range, 17 to 64 years). All subjects reported developing subjective functional changes in their chewing ability such as fatigue. However, in several subjects the bite force did not decrease despite subjective reports of fatigue. Some of these subjects (subjects 10, 14, 22, 27, and 34 in Table 1) registered initial force measurements that were very small (< 2 lb) and could therefore not decrease. The reason for these very low initial measurements in these subjects is not clear. It does not appear to be related to instability of the dentition or pathologic condition of the jaw joints. Subjects did not report changes in subjective chewing ability as adverse events.

Mean subjective pain (Fig 1) is shown to decline from  $T_0$  to  $T_8$ . Decline in ability to generate bite force is evident from  $T_0$  to  $T_2$  (Fig 2). However by  $T_4$ , mean bite force was seen to increase again. By  $T_8$ , the mean bite force had superceded preinjection levels. There was considerable variation in degree of response to the BTX in terms of reduction in pain as well as reduction in bite force (Table 1). However, the time frame for onset of change in outcome measure was relatively consistent between subjects.

A paired *t* test of the difference in mean pain measurements showed significance between  $T_0$  and  $T_2$  ( $P < .0001$ )

and again between  $T_2$  and  $T_4$  ( $P < .05$ ). No further significant decreases in mean pain were found at later time points; however, mean pain reduction remained significantly below baseline ( $P < .0001$ ) throughout the study period. Bite force measurements only showed significant differences between  $T_0$  and  $T_2$  ( $P < .0003$ ) and then between  $T_6$  and  $T_8$  ( $P < .0005$ ). Bite forces at  $T_0$  and  $T_8$  were not statistically different.

Pearson correlation coefficients of pain and bite force measurements at each time point showed only a single significant correlation at  $T_4$  (correlation coefficient, 0.52;  $P < .001$ ). However, this was a weak positive correlation in which a negative correlation would intuitively be expected, suggesting an anomalous finding. No other statistically significant correlation was evident between demographic factors including age, sex, weight, length of time of condition, education level, income level, and pain scores or bite force measurements.

Four of the 35 subjects reported transient adverse events. All occurred before the first follow-up appointment. Three subjects reported moderate bitemporal headaches, which began within 24 hours of the injections and lasted less than 24 hours. These were treated by the subjects with acetaminophen and did not recur. One subject reported slight bruising of the right temple area, which resolved in 3 days.

## Discussion

The mechanism by which BTX-A reduces pain in patients with spastic or nonspastic muscles was originally assumed to be due to muscle relaxation. This was based on what was known about the pharmacologic action of BTX-A, specifically an inhibition of acetylcholine-mediated neuromuscular transmission at the motor end plate.<sup>1</sup> However, anecdotal reports suggested that the degree and duration of pain relief were more profound than could be explained by muscle relaxation alone.<sup>52</sup>

The results of this study showed that both muscle weakening and pain relief occurred at the same time and proportionally during the first 2 weeks after BTX-A injection (Fig 3). However, the only statistically significant correlation between pain and bite force was noted at  $T_4$ , as the bite force increased. From a statistical analysis perspective, there was no relationship between bite force and subjective pain measurement. All the correlation coefficients but one were not only not significant, but they were all positive, which would be against expectations. The correlation at time  $T_4$ , although reaching significance (correlation coefficient, 0.52;  $P < .001$ ), must still be due to chance, because there is no reasonable explanation for having a better ability to bite with higher pain (positive correlation).

By 2 months after injection ( $T_8$ ), mean bite force exceeded the baseline value but mean pain reduction was still very evident. The paired *t* test of the difference of the means for pain clearly demonstrated a significant decrease in pain from baseline, which was maintained throughout the study period. This has been demonstrated in a previous study with similar methodology<sup>19</sup> and suggests a definite analgesic effect. The mean bite

**Table 1. Raw Scores: Pain (VAS) and Bite Force**

SUBJECT	PAIN VAS (0-10)					BITE FORCE (POUNDS)				
	T0	T2	T4	T6	T8	T0	T2	T4	T6	T8
1	9	1	1	0	0	14	10	11	18	20
2	8	5	5	4	4	32	24	14	18	22
3	8	8	8	1	1	25	27	21	30	30
4	8	8	8	7	3	13	6	14	11	34
5	9	2	2	1	1	16	9	11	14	18
6	9	9	9	7	4	30	10	28	15	15
7	6	0	0	2	2	14	4	6	9	10
8	7	4	4	6	5	15	12	12	10	14
9	8	6	6	4	5	8	7	6	7	9
10	7	8	5	3	2	2	2	8	4	10
11	8	4	3	1	1	5	6	9	10	12
12	9	8	6	6	6	12	8	9	17	20
13	7	7	8	3	7	37	24	22	20	37
14	9	5	5	2	1	2	2	4	7	14
15	4	2	4	4	3	15	11	11	17	17
16	6	5	3	4	2	10	11	12	14	15
17	9	7	5	5	6	8	5	5	15	13
18	8	8	5	5	5	37	37	14	18	20
19	3	3	4	1	0	9	3	1	1	1
20	8	7	7	3	6	18	15	9	11	12
21	7	5	5	6	3	18	20	8	5	12
22	7	7	6	3	2	1	5	5	0	5
23	8	6	6	6	6	20	1	18	13	20
24	7	4	4	5	5	3	2	3	7	3
25	9	7	7	8	6	14	7	9	11	10
26	8	9	7	6	5	12	6	10	14	15
27	3	1	1	1	1	1	1	1	1	1
28	4	3	2	1	1	3	1	1	2	1
29	9	4	4	7	7	17	20	11	1	8
30	8	5	5	5	4	8	8	5	8	6
31	9	9	7	9	8	22	13	15	13	20
32	9	6	5	7	5	11	10	7	10	16
33	7	1	4	7	7	11	4	7	9	9
34	9	3	2	2	3	1	1	14	11	15
35	5	5	4	1	1	7	5	12	12	17
Mean	7.4	5.2	4.8	4.1	3.7	13.5	9.7	10.1	10.9	14.3
Standard deviation	1.8	2.6	2.2	2.5	2.3	9.8	8.5	6.0	6.3	8.4
Standard error of mean	0.3	0.4	0.4	0.4	0.4	1.7	1.4	5.9	1.1	1.4
Percent of T <sub>0</sub>	100	70	64	55	50	100	72	75	81	106

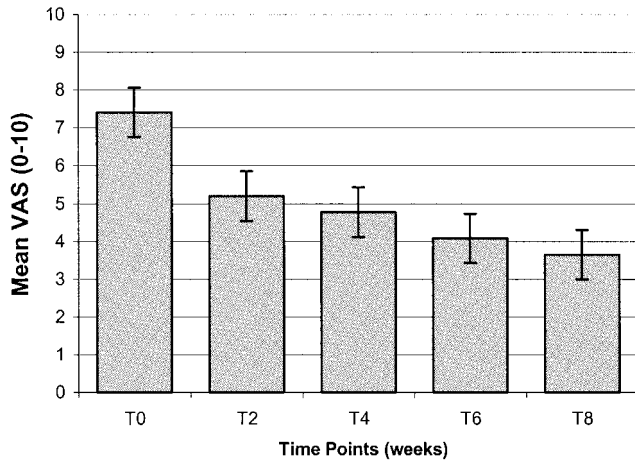
VAS, Visual Analogue Scale.

force changes were significantly different only between the baseline and the first postinjection measurement and again between the fourth and fifth ( $T_4$ ) measurements (Fig 2). This finding is not unexpected given the transient muscle relaxing properties of BTX-A. However, the lack of correlation between pain and muscle strength suggests that their initial simultaneous decrease may be coincident rather than causal. It would appear that there are 2 separate but coexisting processes occurring after injection with BTX-A, one process related to pain and another related to muscular relaxation.

The treatment of torticollis with BTX further underscores the apparent dichotomy between muscle function and pain. Spasmodic torticollis is one of the more common forms of focal head and neck dystonia. It is an often

hereditary, centrally driven condition involving contraction of one of the longitudinal neck muscles, frequently the sternocleidomastoid. This long-term condition with variability in the intensity of the muscular spasm may result in postural changes to the head and shoulder as well as considerable local pain.<sup>40</sup> Treating this condition with BTX-A injections relieves both the excessive muscular tension as well as the local pain. As previously noted, this is a condition in which the degree of pain relief is considered to be out of proportion to the relief of muscle spasm.<sup>6,7</sup>

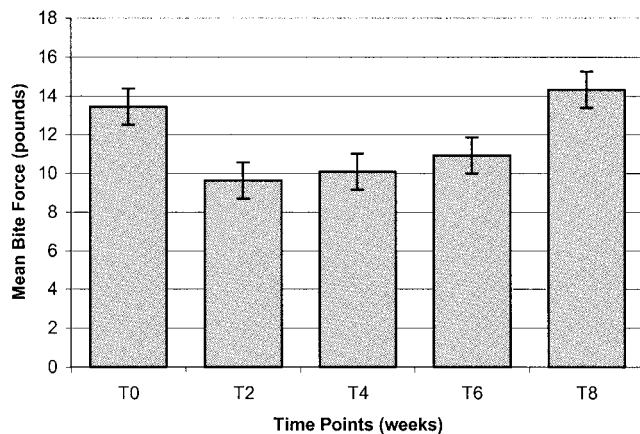
Myogenous pain associated with conditions of aberrant muscle activity has historically been assumed to be a function of the muscular spasm or hyperactivity. Travell et al<sup>51</sup> and subsequently others<sup>12,16</sup> have suggested that



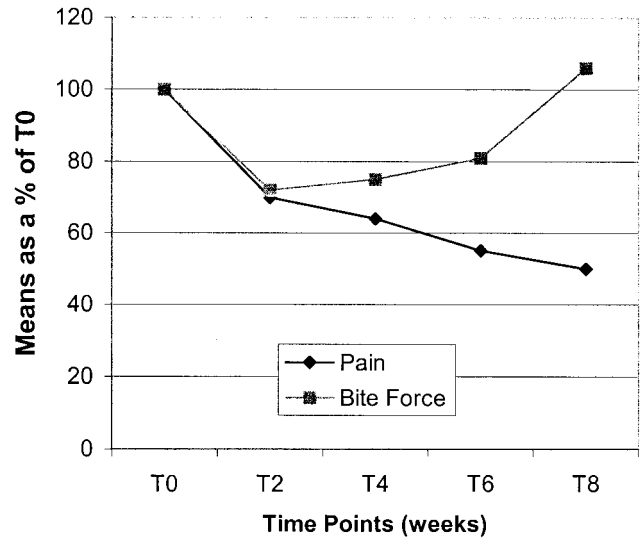
**Figure 1.** Change in mean VAS pain scores from baseline (T<sub>0</sub>) to T<sub>8</sub>.

muscle hyperactivity leads to fatigue, spasm, and pain, which reinforce further myospasm, resulting in a positive feedback loop. This theory, although attractive and logically acceptable, has never enjoyed strong objective support, particularly in chronically painful conditions.<sup>29</sup> Short-term muscle pain such as postexertion pain can be explained in terms of ischemia and acidosis resulting in the release of inflammatory mediators and pain-inducing neuropeptides. These proteins in turn bind to receptors (nociceptors) on afferent sensory nerves within the muscle and associated with blood vessels signaling pain.<sup>9,22,45</sup> This mechanism for acute pain may be involved in chronic muscle-associated pain; however, because of the relatively short-term nature of most inflammatory processes it is not likely the only mechanism. No other satisfactory alternatives have been advanced.<sup>14,34,46</sup>

As soft tissue pain conditions become more chronic, the distinction between muscle pain and myofascial pain becomes less clear. Myofascial pain conditions differ from dystonias in that there is no true muscular spasm. "Taut bands," "trigger points," and tender areas within myofascial tissues are a characteristic finding; however, their pathophysiologic significance in myofascial pain is



**Figure 2.** Change in mean bite force from baseline (T<sub>0</sub>) to T<sub>8</sub>.



**Figure 3.** A composite graph showing change in mean pain score and mean bite force after injection with BTX-A (T<sub>0</sub>). Mean VAS scores and mean bite force are expressed as a percentage of T<sub>0</sub>. The only statistically significant correlation between these curves is at T<sub>4</sub>.

unclear.<sup>21</sup> The actual source of pain in myofascial conditions may be different than in muscle pain conditions such as dystonias, in which pain is attributed to muscle contraction, tendon and joint tension, nerve root compression, or extremes of posture.<sup>37</sup> Although there has been no definitive explanation as to how myofascial pain originates, some evidence suggests a dysfunction of the muscle spindle system resulting in aberrant sensory stimulation.<sup>38</sup> Other proposed mechanisms include peripheral sensitization through the stimulation of silent afferent sensory nerves by neuroinflammatory mediators.<sup>34</sup>

On the basis of the premise that most myofascial pain conditions have some muscular involvement, studies were initiated to test whether BTX-A could be an effective form of therapy. Two small, published trials examining the efficacy of BTX-A in cervicothoracic myofascial pain have reported mixed results. It is uncertain from these studies whether clinical failures with BTX therapy were due to deficiencies in injection protocol or whether the myofascial pain patients being treated in these studies were a pathophysiologically inhomogeneous group.<sup>39,53</sup>

For the purposes of this study, subjects with TMD provided a relatively homogenous myofascial condition in which muscle function could easily be measured. To further reduce confounding factors, a specific subgroup of the TMD population was selected. These were the individuals in whom chronic pain could be ascribed to the clenching muscles alone, specifically the masseter muscle on one or both sides. In this way the potential disparity between muscle pain<sup>34</sup> and myofascial pain<sup>21</sup> might be minimized.

TMD is a collective term used to describe a group of conditions involving the temporomandibular joint, masticatory muscles, as well as associated structures. It is considered to be one of the more common head and neck



myofascial conditions, affecting approximately 10% of the Western population.<sup>41</sup> Etiologic factors identified for all types of TMD include masticatory muscle activity, trauma, psychologic factors, and systemic diseases such as arthritis.<sup>8,11,15,20</sup> The role of occlusion remains uncertain.<sup>2</sup> Treatment of muscle-centered TMD (as opposed to TMD variants that involve joint pathologic conditions) is most commonly treated with physical modalities such as orthotic devices, physiotherapy, and massage. Recently, BTX-A has also shown some effectiveness in treating this condition.<sup>5,18,19</sup>

BTX-A, 1 of 8 subtypes of a potent biologic toxin produced by *Clostridium botulinum*,<sup>48</sup> is a presynaptic neurotoxin.<sup>13</sup> It has been shown to cause a dose-dependent weakness or paralysis in skeletal muscle by blocking the Ca<sup>++</sup> mediated release of acetylcholine from motor nerve endings.<sup>31</sup> The primary effect in muscle is on alpha motor neuron function, but BTX-A may also affect the gamma motor neurons in the muscle spindles,<sup>17</sup> resulting in lower muscle resting tone. Reversal of local paralysis occurs initially by neural sprouting with reinnervation of the muscle<sup>23</sup> and ultimately by regeneration of the acetylcholine vesicle docking proteins,<sup>5</sup> which restores function in 1 to 4 months.

The mechanistic basis for the reported analgesic effect of BTX-A injected into muscle tissue is still speculative; however, it is likely that more than one mechanism is involved. Animal data with the rat hind paw model<sup>10</sup> and the guinea pig conjunctiva model<sup>35</sup> have shown a dose-related anti-inflammatory effect attributable to BTX-A. The reduction in inflammation is not absolute, and the protective effect is not long-lasting but is appreciable in these animal challenge studies. Borodic et al<sup>5</sup> report on the effect of BTX-A in cholinergic urticaria syndrome in humans. This condition, brought on by exertion, has a characteristic localized skin reaction, which includes the formation of punctuate hives with itching and redness attributable to histamine release and mast cell degranulation. They note that the usual erythematous skin changes seen during an acute exacerbation of the condition are absent in areas injected with BTX-A. This strongly suggests that BTX-A is able to block the cutaneous vasodilatation and the concomitant inflammatory response.

Other animal work has shown that the release of pain modulating neurotransmitters such as calcitonin gene-related protein (CGRP), which is associated with primary afferent nerve fibers in muscle and blood vessel endothelium,<sup>14,42</sup> can be inhibited by BTX-A.<sup>26,36,50</sup> Work by Saldhana et al<sup>43</sup> in human headache sufferers has demonstrated nerve growth factor mediated release of CGRP from sensory nerve fibers associated with inflamed temporal arteries. They suggest that the neurogenic inflammatory response associated with the release of CGRP in endothelial nerves may be a central factor in the mechanism of vascular head pain. Therefore if BTX-A can inhibit neuropeptide release (such as CGRP) in humans as it does in animal model systems, then a potential explanation for its peripheral anti-inflammatory effect exists. Such a mechanism may help account for the reported

efficacy of BTX-A in treating headaches affecting the trigeminovascular system.<sup>3,30</sup>

The relationship between inflammation and chronic myofascial pain is not completely understood. However, it is known that nonspecific inflammatory mediators and neuropeptides have individual modulating and sensitizing effects on nociceptive pathways.<sup>9,22,25</sup> Silent nociceptors that normally have a threshold above a normal operating range can be sensitized to selectively respond at a lower threshold by an inflammatory or hypoxic process.<sup>25,32,33</sup> These physiochemical interactions are cascade-like and therefore may produce conditions that favor maintenance of nociceptor discharge with minimal stimulation.<sup>27,28,34,49</sup>

Central mechanisms are also contributory to chronic myofascial pain. In the trigeminal system, central nociceptive pathways are associated with 2 main types of neurons in subnucleus caudalis. Wide dynamic range neurons are responsive to noxious and non-noxious stimuli as well as nociceptive specific neurons.<sup>44</sup> Peripheral nociceptive pathways converge on these neurons producing overlapping receptive fields, which can dynamically interact.<sup>34,45,47</sup> Therefore a peripheral sensory field, which has been sensitized through a process such as inflammation, can alter the function of central neurons. Described as central neuroplasticity, this phenomenon can change the size and sensitivity of a receptor field to stimulation, suggesting that even non-noxious peripheral stimulation can be interpreted as pain.<sup>24,34,45</sup>

A direct analgesic action of BTX-A may therefore be related to its influence on inflammation leading to diminished peripheral sensitization. Although there is no specific evidence supporting it, it is conceptually attractive to consider that the indirect analgesic actions of BTX-A may be those of diminishing afferent input to the central nervous system. Possible mechanisms by which this may occur include reduced proprioceptive information through inhibition of gamma motor neurons in the muscle spindles<sup>17</sup> and indirectly by reduced physical stimulation of peripheral tissues as a result of reduced muscle tone.

The evidence, although sparse and inconclusive at present, suggests that the observed analgesic properties of BTX-A are mechanistically more complex than simple muscular relaxation. The observations presented in this and other studies raise the possibility of a complex interaction of the toxin within the peripheral tissues and potentially indirect influences on central pain mechanisms.

## Conclusions

No definitive conclusions can be drawn from this study. However, the data add further evidence that the analgesic effects of BTX-A do not correlate with and may therefore be independent of muscle relaxation.

## Acknowledgments

We would like to thank Professor A. Csima, University of Toronto Department of Biostatistics, for her help in analyzing the data and providing statistical expertise.

## References

1. Aoki R: The development of Botox: Its history and pharmacology. *Pain Digest* 8:337-341, 1998
2. Bales JM, Epstein JB: The role of malocclusion and orthodontics in temporomandibular disorders. *J Can Dent Assoc* 60:899-906, 1994
3. Binder WJ, Brin MF, Blitzer A, Schoenrock LD, Pagoda JM: Botulinum toxin type A (Botox) for treatment of migraine headaches: An open label study. *Otolaryngol Head Neck Surg* 123:669-676, 2000
4. Blanksana NG, van Eijden TM: EMG heterogeneity in human temporalis and masseter muscle during static biting, open/close excursions and chewing. *J Dent Res* 74:1318-1327, 1995
5. Borodic GE, Acquadro M, Johnson EA: Botulinum toxin therapy for pain and inflammatory disorders: Mechanisms and therapeutic effects. *Expert Opin Investig Drugs* 10:1531-1544, 2001
6. Brin MF, Fahn S, Moskowitz C, Friedman A, Shale HM, Greene PE, Blitzer A, List T, Lange D, Lovelace RE: Localized injections of botulinum toxin for the treatment of focal dystonia and hemifacial spasm. *Mov Disord* 2:237-254, 1987
7. Comella CL, Jankovic J, Brin MF: Use of botulinum toxin type A in the treatment of cervical dystonia. *Neurology* 55(Suppl 5):S15-S21, 2000
8. Carlsson GE: Epidemiological studies of signs and symptoms of temporomandibular-joint-pain-dysfunction: A literature review. *Austr Prosthodont Soc Bull* 14:7-12, 1984
9. Cuello AC: Peptides as neuromodulators in primary sensory neurons. *Neuropharmacology* 26:971-979, 1987
10. Cui M, Aoki R: Botulinum toxin type-A reduces inflammatory pain in the rat formalin model. *Cephalalgia* 20:41, 2000
11. DeLeeuw R, Boering G, Stegenga B, deBont LGM: Clinical signs of TMJ osteoarthritis and internal derangement 30 years after non-surgical treatment. *J Orofac Pain* 8:18-24, 1994
12. Dorpat TL, Holmes TH: Backache of muscle tension origin. In: Kroger WS (ed): *Psychosomatic Obstetrics Gynecology and Endocrinology*. Springfield, IL, CC Thomas, 1962, 425-436
13. Drachman AB: Atrophy of skeletal muscle in chick embryos treated with botulinum toxin. *Science* 14:719-721, 1964
14. Dubner R, Sessle BJ, Storey AT: *The Neural Basis of Oral and Facial Function*. New York, NY, Plenum, 1978, pp 483
15. Dworkin SF. Behavioral characteristics of chronic temporomandibular disorders: Diagnosis and treatment, in Sessle BJ, Bryant PS, Dionne RA (eds): *Progress in Pain Research and Management*, vol 4. Seattle, WA, IASP Press, 1995, pp 175-192
16. Emre M, Mathies H. *Muscle Spasms and Pain*, Park Ridge, NJ, Parthenon, 1988
17. Filippi GM, Errico P, Santarelli R, Bagolini B, Manni E: Botulinum A toxin effects on rat jaw muscle spindles. *Acta Otolaryngol* 113:400-404, 1993
18. Freund B, Schwartz M: Botulinum toxin in the treatment of TMD: A pilot study. *Oral Health* 88:32-37, 1998
19. Freund B, Schwartz M, Symington J: The use of botulinum toxin for the treatment of temporomandibular disorders: Preliminary findings. *J Oral Maxillofac Surg* 57:916-921, 1999
20. Friction J, Kroening R, Haley D, Siegert R: Myofascial pain and dysfunction of the head and neck: A review of clinical characteristics of 164 patients. *Oral Surg Oral Med Oral Pathol* 57:615-627, 1985
21. Friction JR: Myofascial pain and whiplash. *Spine* 7:403-421, 1993
22. Hargreave KM, Roszkowski MT, Jackson DL, Bowles W, Richardson JD, Swift JQ: Neuroendocrine and immune responses to injury, degeneration and repair. In: Sessle BJ, Bryant PS, Dionne RA (eds): *Progress in Pain Research and Management*, vol 4: *Temporomandibular Disorders and Related Pain Conditions*. Seattle, WA, IASP Press, 1995, 273-292
23. Holds JB, Alderson K, Fogg SG, Anderson RL: Motor nerve sprouting in human orbicularis muscle following botulinum toxin A injection. *Invest Ophthalmol Vis Res* 31:964-967, 1990
24. Hylden JLK, Nahin RL, Traub RJ, Dubner R: Expansion of receptive fields of spinal lamina 1 projection neurons in rats with unilateral adjuvant induced inflammation: The contribution of dorsal horn mechanisms. *Pain* 37:229-243, 1989
25. Hu JW: Cephalic myofascial pain pathways. In: Olesen J, Schoenen J (eds): *Tension-type Headache: Classification, Mechanisms and Treatment*. New York, NY, Raven Press Ltd, 1993, 69-77
26. Jung HH, Lauterburg T, Burgunder JM: Expression of neurotransmitter genes in rat spinal motoneurons after chemodenervation with botulinum toxin. *Neuroscience* 78:469-479, 1997
27. Levine JD, Taiwo YO, Collins SD, Tam JK: Noradrenalin hyperalgesia is mediated through interaction with sympathetic postganglionic neuron terminals rather than activation of primary afferent nociceptors. *Nature* 323:158-160, 1986
28. Lotz M, Carson DA, Vaughn JH: Substance P activation of rheumatoid synoviocytes: Neural pathway in pathogenesis of arthritis. *Science* 235:893-895, 1987
29. Lund JP, Donga R, Widmer CG, Stohler CS: The pain adaptation model: A discussion of the relationship between chronic musculoskeletal pain and motor activity. *Can J Physiol Pharmacol* 69:683-694, 1991
30. May A, Goadsby PJ: The trigeminovascular system in humans: Pathophysiologic implications for primary headache syndromes of neural influences on the cerebral circulation. *J Cereb Blood Flow Metab* 19:115-127, 1999
31. Melling J, Hambleton P, Shone CC. Clostridium botulinum toxins: Nature and preparation for clinical use. *Eye* 2(pt 1):16-23, 1988
32. Mense S, Meyer H: Bradykinin induced modulation of the response behavior of different types of feline group III and IV muscle receptors. *J Physiol* 398:49-63, 1988
33. Mense S: Considerations concerning the neurobiological basis of muscle pain. *Can J Physiol Pharmacol* 69:610-616, 1991
34. Mense S: Nociception from skeletal muscle in relation to clinical muscle pain. *Pain* 54:241-289, 1993
35. Merayo-Llodes J, Calonge M, Foster C: Experimental

model of allergic conjunctivitis to ragweed in guinea-pig. *Curr Eye Res* 14:487-494, 1995

36. Meunier FA, Colasante C, Faille L, Gastard M, Molgo J: Upregulation of calcitonin gene-related peptide at mouse motor nerve terminals poisoned with botulinum type-A toxin. *Pflugers Arch* 431(Suppl 2):R297-R298, 1996

37. O'Brien CF: Clinical applications of botulinum toxin: Implications for pain management. *Pain Digest* 8:342-345, 1998

38. Porta M, Perretti A, Gamba M, Luccarelli G, Fornari M: The rational and results of treating muscle spasm and myofascial syndromes with Botulinum toxin type A. *Pain Digest* 8:346-352, 1998

39. Porta M: A comparative trial of botulinum toxin type A and methylprednisolone for the treatment of myofascial pain syndrome and pain from chronic muscle spasm. *Pain* 85:101-105, 2000

40. Richardson E, Beal MF, Martin JB: Degenerative disease of the nervous system, in Braunwald E, Isselbacher KJ, Petersdorf RG, Wilson JD, Martin JB, Fauci AS (eds): *Harrison's Principles of Internal Medicine* (11th edition). New York, NY, McGraw Hill, 1987, pp 2020-2021.

41. Rugh JD, Solberg WK: Oral health status in the United States: Temporomandibular disorders. *J Dent Educ* 49:398-406, 1985

42. Sala C, Andreose JS, Fumagalli G, Lomo T: Calcitonin gene-related peptide: Possible role in formation and maintenance of neuromuscular junctions. *J Neurosci* 15:520-528, 1995(Pt 2)

43. Saldanha G, Hongo J, Plant G, Acheson J, Levy I, Anand P: Decreased CGRP, but preserved Trk A immunoreactivity in nerve fibres in inflamed human superficial temporal arteries. *J Neurol Neurosurg Psychiatry* 66:390-392, 1999

44. Sessle BJ, Hu JW, Amano N, Zhong G: Convergence of cutaneous, tooth pulp, visceral, neck and muscle afferents into nociceptive and non-nociceptive neurons in trigeminal

subnucleus caudalis (medullary dorsal horn) and its implications for referred pain. *Pain* 27:219-253, 1986

45. Sessle BJ: Biological & psychological aspects of orofacial pain. in Stohler CS, Carlson DS (eds): *Craniofacial Growth Series* 29. Ann Arbor, MI, Center for Human Growth & Development, The University of Michigan, 1994

46. Sessle BJ: Masticatory muscle disorders: Basic science perspectives. In: Sessle BJ, Bryant PS, Dionne RA (eds): *Progress in Pain Research and Management*, vol 4: Temporomandibular Disorders and Related Pain Conditions. Seattle, WA, IASP Press, 1995, 47-61

47. Shigenga Y, Sera M, Nishimori T: The central projection of masticatory afferent fibres to the trigeminal sensory nuclear complex and upper cervical spinal cord. *J Comp Neurol* 268:489-507, 1988

48. Simpson LL: The origin, structure, and pharmacological activity of botulinum toxin. *Pharmacol Rev* 33:155-188, 1981

49. Taiwo YO, Bjerknes LK, Goetzl EJ, Levine JD: Mediation of primary afferent peripheral hyperalgesia by the cAMP second messenger system. *Neuroscience* 32:577-580, 1990

50. Tarabal O, Caldero J, Ribera J, Sorribas A, Lopez R, Molgo J, Esquerda JE: Regulation of motoneuronal calcitonin gene-related peptide (CGRP) during axonal growth and neuromuscular synaptic plasticity induced by botulinum toxin in rats. *Eur J Neurosci* 8:829-836, 1996

51. Travell JG, Rinzler S, Herman M: Pain and disability of the shoulder and arm: Treatment by intramuscular infiltration with procaine hydrochloride. *JAMA* 120:417-422, 1942

52. Watanabe Y, Bakheit A, McLellan D: A study of the effectiveness of botulinum toxin type A (Dysport) in the management of muscle spasticity. *Disabil Rehabil* 20:62-65, 1998

53. Wheeler AH, Goolkasian P, Gretz SS: A randomized double blind, prospective study of botulinum toxin injection for refractory, unilateral, cervicothoracic, paraspinal, myofascial pain syndrome. *Spine* 23:1662-1666, 1998