Topics in
PAIN MANAGEMENT

Vol. 27, No. 1 | Current Concepts and Treatment Strategies | August 2011

CME ARTICLE

Temporomandibular Disorder: A Review of Current Standard Treatment Modalities

Angela McWilliams, MD, and Stelian Serban, MD

Learning Objectives: After participating in this CME activity, the physician should be better able to:

1. Describe the pathophysiology of temporomandibular disorder.
2. Evaluate a patient with symptoms of temporomandibular disorder and make a differential diagnosis.
3. Assess current treatment modalities and their applications to specific etiologies of temporomandibular disorder.

Temporomandibular joint (TMJ) *disorder* is a collective term that includes a number of symptoms involving the muscles of mastication, the TMJ, or the surrounding orofacial structures. It is the second leading cause of nondental orofacial pain after trigeminal neuralgia. The muscles of mastication—rather than the TMJ—are the most common origin of orofacial pain; indeed, TMJ disorder is considered to be a musculoskeletal disorder. To distinguish between the joint and muscular origins of temporomandibular pain, the American Dental Association has suggested the name of temporomandibular disorder in place of TMJ disorder. The term *temporomandibular disorder* emphasizes that temporomandibular pain includes pain of either muscular or joint origin, or both.[1]

The TMJ, composed of the squamous portion of the temporal bone and the condyle of the mandibular bone, connects the mandible to the skull. It is a loose-fitting, sliding and rotational joint covered in fibrous cartilage with an intervening fibrous disc in between, referred to as a modified hinge-type synovial joint. The joint contains 2 synovial membranes: the superior synovial joint lining the superior part of the articular disc and inferior synovial membrane lining the inferior portion of the articular disc. The mandible is connected to the cranium by 2

In This Issue

Dr. McWilliams is Fellow in Pain Management, and Dr. Serban is Assistant Professor of Anesthesiology and Pain Management, Mount Sinai School of Medicine, Box 1010, One Gustave Levy Plaza, New York, NY 10029; E-mail: elzfrost@aol.com.

All faculty and staff in a position to control the content of this CME activity and their spouses/life partners (if any) have disclosed that they have no financial relationships with, or financial interests in, any commercial companies pertaining to this educational activity.

Lippincott Continuing Medical Education Institute, Inc., is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Lippincott Continuing Medical Education Institute, Inc., designates this enduring material for a maximum of 1.5 *AMA PRA Category 1 Credits*™. Physicians should only claim credit commensurate with the extent of their participation in the activity. To earn CME credit, you must read the CME article and complete the quiz and evaluation assessment survey on the enclosed form, answering at least 70% of the quiz questions correctly. This activity expires on July 31, 2012.

extrinsic ligaments and 1 lateral ligament. The sphenomandibular ligament functions as a passive support and the main weight bearer of the TMJ. Of note, the stylomandibular ligament contributes a very small amount to the strength of the joint.

There are wide differences of opinion regarding the etiology, pathophysiology, and treatment of TMJ disorder.

The muscles of mastication are responsible for the movement of the TMJ. The masseter, temporal, and medial pterygoid muscles elevate the mandible and result in closure of the mouth (Fig. 1). The lateral pterygoid, masseter, and medial pterygoid muscles produce protrusion of the lower jaw. Retrusion causes retraction of the lower jaw and is produced by the temporal and masseter muscles. The ipsilateral retractors and contralateral protruders produce lateral movement of the joint. All the muscles of mastication are innervated by the mandibular nerve, a branch of the trigeminal nerve.[1,2]

Physicians completing this CME activity will not only understand how to evaluate the anatomy of the temporomandibular joint, but will also be better able to diagnose the symptoms of temporomandibular disorder, make differential diagnoses, and assess current treatment options they can apply to practice.

Causes of TMJ Pain

Studies have failed to consistently demonstrate a specific cause of temporomandibular disorder in most cases. There

The continuing education activity in *Topics in Pain Management* is intended for clinical and academic physicians from the specialties of anesthesiology, neurology, psychiatry, physical and rehabilitative medicine, and neurosurgery as well as residents in those fields and other practitioners interested in pain management.

Wolters Kluwer Health | Lippincott Williams & Wilkins

Topics in Pain Management (ISSN 0882-5646) is published monthly by Lippincott Williams & Wilkins, 16522 Hunters Green Parkway, Hagerstown, MD 21740-2116. **Customer Service: Phone (800) 638-3030, Fax (301) 223-2400, or Email customerservice@lww.com**. Visit our website at **lww.com.**

 Priority postage paid at Hagerstown, MD, and at additional mailing offices. GST registration number: 895524239. POSTMASTER: Send address changes to *Topics in Pain Management*, Subscription Dept., Lippincott Williams & Wilkins, P.O. Box 1600, 16522 Hunters Green Parkway, Hagerstown, MD 21740-2116.

Publisher: Randi Davis

Subscription rates: *Personal:* $256 US, $358.50 Foreign. *Institutional:* $492 US, $594.50 Foreign. *In-training:* $116 US, $144.50 Foreign. *Single copies:* $49. Send bulk pricing requests to Publisher.

Topics in Pain Management is indexed by SIIC (Sociedad Iberoamericana de Información Científica).

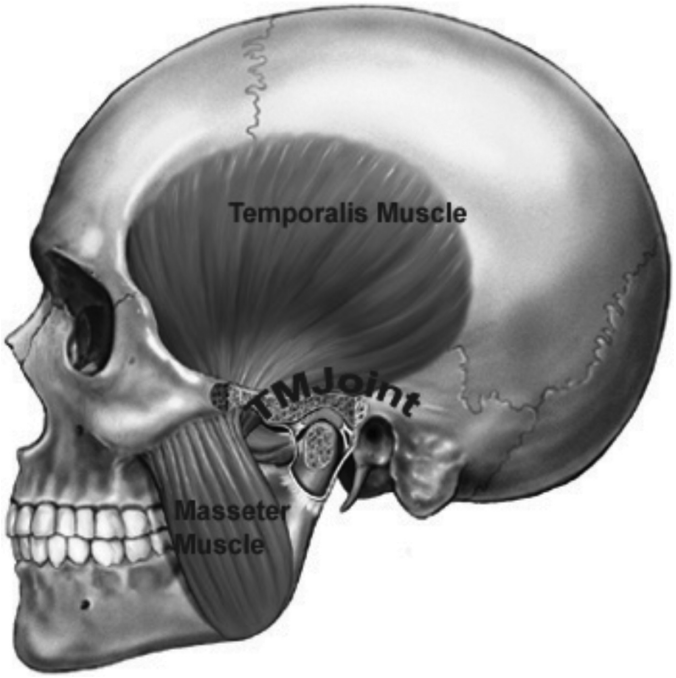

Figure 1. The muscles of mastication are shown surrounding the TMJ.

are wide differences of opinion throughout various specialties with regard to the etiology, pathophysiology, and treatment of the disorder. Proposed etiologies of TMJ disorder include trauma, rheumatologic disease, or advanced age.

Trauma to the TMJ can be further broken down into macro and micro traumas. Macrotrauma is a result of external blunt-force injury to the jaw. Microtrauma is due to internal joint injury from jaw-clenching or teeth-grinding. The TMJ may also be subject to habitual dislocation that manifests with excessive forward motion of the condyle, to the point of complete separation of the articular surfaces with permanent fixation.

Rheumatologic etiologies include osteoarthritis and rheumatoid arthritis. Osteoarthritis can affect the jaw joint by the same mechanism that affects other joints, that is, causing joint breakdown progressing with age. Repetitive micro and macro traumas accelerate osteoarthritic changes. Rheumatoid arthritis is an autoimmune multisystem inflammatory disorder that may cause inflammation affecting the TMJs symmetrically, as is characteristic of the disease in other joints of the body.[3]

Pain in the orofacial area is the defining feature of TMJ disorder.

Masticatory muscle disorders may be caused by overuse from chewing, swallowing, speaking, or muscle spasm. Muscular pain, or "malia," caused by increased muscle use may occur secondary to an increased level of metabolic waste products and vasoconstriction. Vasoconstriction causes a decreased deliverance of nutrient blood blow and decreased removal of waste products. The metabolic waste products that are thought to be the source of pain are mainly bradykinins and prostaglandins.[2] There may also be a component of centrally mediated pain manifesting as pain in the orofacial jaw area.

Symptoms

Pain in the orofacial area is the defining feature of this disorder. TMJ disorder typically affects young women in the third and fourth decades of life. Most individuals seek medical care within 1 month of symptoms. After 3 months of continuous pain, the disorder is considered chronic. Jaw and facial pain most often are bilateral and may have radiation of pain to the neck and shoulders. Orofacial pain is exacerbated by light or deep touch, talking, chewing, or yawning. Temporomandibular disorder may be reported initially as periauricular pain with associated tinnitus and hearing loss. There may be swelling of the affected side of the face from inflamed tissues surrounding the joint. Crepitus may be felt if there is a component of osteoarthritis or wearing down of the articular cartilages from remodeling. Patients may report decreased range of motion or painless "clicking" of the jaw.

Differential Diagnosis

Several other conditions may mimic the pain of TMJ disorder, including the following:

- Temporomandibular disorder, which includes both muscular and joint origins;
- Episodic neuropathic pain;
- Continuous neuropathic pain;
- Trigeminal neuralgia;
- Raeder syndrome (paratrigeminal neuralgia);
- Ramsay Hunt syndrome (varicella/zoster auricular syndrome);
- Migraine;
- Tension-type headache;
- Dental caries/abscesses; and
- Oromaxillary cancer.

Careful history and physical examination should be undertaken to rule out these possible causes of facial pain.

Treatment

Depending on the individual presentation, therapeutic modalities include conservative, pharmacologic, or interventional approaches.

- Conservative management includes patient education, reassurance, psychotherapy, behavioral therapy, and pharmacotherapy.

- Interventional methods include injections, arthrocentesis, arthroscopy, and arthrotomy.
- Pharmacologic treatment includes use of a single agent or a multimodal approach.

Patient education, psychotherapy, and behavioral therapy target patients with known underlying anxiety or other psychologic symptoms that lead the individual to clench and grind teeth. Relaxation techniques and biofeedback are the recommended general starting point for this patient population. Pharmacotherapy is suggested by multiple sources in the literature to be successful in a large number of cases. The question of which pharmacologic agent to choose should be decided for individual patients, on the basis of coexisting comorbidities.

After 3 months of continuous pain, TMJ disorder is considered chronic.

Physiotherapy involves application of ice packs, passive and active stretching of the TMJ, and treatment of trigger points. Variable outcomes of the effectiveness in the short and long terms have been reported. Trigger-point injections of the muscles of mastication have been tried including dry needling and use of local anesthetics with and without corticosteroids. Such therapies have not generally demonstrated good results in this patient population.[1]

Surgical management of temporomandibular disorder may be beneficial in individuals with severe arthritis in the joint. For the TMJ, arthrocentesis or arthroscopy is the common procedure performed. Surgery is indicated in the management of fractures, infections, and tumors of the joint.[4]

Pharmacologic therapy includes the use of several medications, combining single-agent and multiagent therapies. In general, anti-inflammatory drugs including, but not limited to, aspirin, ibuprofen, naproxen, piroxicam, and prednisone are used as treatment initially for mild pain symptoms. Opioids may be indicated to treat moderate to severe pain symptoms.

Several studies have analyzed the effectiveness of drug trials and are summarized as follows:

Oral Benzodiazepine Versus Placebo

The study included 20 participants in a double-blind randomized trial over 60 days. Participants were given 0.25 to 1 mg orally daily. There was no significant statistical difference between clonazepam and placebo in pain reduction.[5]

Gabapentin Versus Placebo

A total of 44 participants were included in a double-blind, randomized trial over 12 weeks. Doses ranged from 300 to 2400 mg once daily. The results demonstrated a statistically significant effect over placebo and showed a reduction of spontaneous pain.[6]

Topical Capsaicin Versus Placebo

The study included 30 participants in a double-blind randomized control trial over 4 weeks. Cream concentration of 0.025% was applied 4 times daily to the painful area. The study failed to demonstrate a significant statistical difference between placebo and topical applications of capsaicin in pain reduction.[7]

Diclofenac Sodium Oral Versus Placebo

A total of 32 participants were included in this double-blind randomized controlled trial over 2 weeks. Doses of 50 mg thrice daily for the first week, and then 50 mg twice daily for the second week, were administered. No statistically significant difference was determined in daily pain scores.[8]

Oral Naproxen and Celecoxib Versus Placebo

Three parallel groups were arranged in this study. A total of 68 patients were included in the double-blind randomized controlled trial over 6 weeks. Naproxen doses of 500 mg twice daily showed a statistically significant difference in the reduction of pain. Celecoxib doses of 100 mg twice daily failed to demonstrate a statistically significant difference in comparison with the placebo.[9]

Topical Methyl Salicylate Versus Placebo

This study included 52 participants in a double-blind randomized controlled trial for 52 days. Cream formulation was applied over the masseter area twice daily. Oral doses of 750/600 mg of glucosamine/chondroitin sulfate were given twice daily. There was a demonstrable reduction in spontaneous pain.[10]

Clonazepam Versus Placebo and Cyclobenzaprine Versus Placebo

A total of 41 participants were included in this double-blind randomized controlled trial for 3 weeks. Clonazepam daily doses of 0.5 mg and cyclobenzaprine daily doses of 10 mg were used. There was no statistically significant effect in either medication. Both agents failed to reduce pain in comparison with placebo.[11]

Oral Glucosamine/Chondroitin Sulfate Versus Placebo

This study included 45 participants in a double-blind randomized controlled trial over 12 weeks. A statistically significant difference in reduction of pain could not be demonstrated.[12]

Piroxicam Versus Placebo and Diazepam Versus Placebo

The study included 41 participants arranged as a double-blind study over 15 days. The doses included 20 mg of piroxicam and 2 mg of diazepam administered as once-daily doses. Three parallel groups were arranged, including pharmacotherapy versus placebo. No statistically significant difference was demonstrated between piroxicam or diazepam versus placebo.[13]

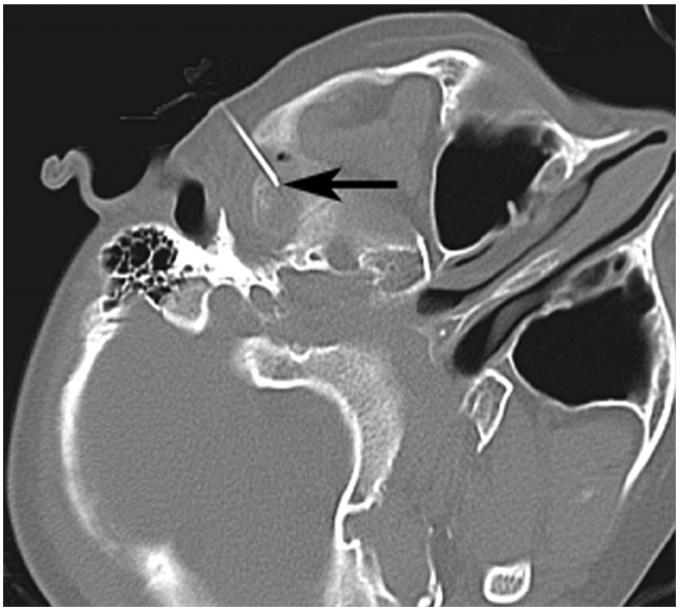

Figure 2. CT-guided TMJ botulinum toxin administration. Needle tip (*arrow*) shows the correct position in the TMJ before botulinum injection.

Prazepam Versus Placebo

This study included 3 groups of patients who received 5 or 10 mg of the drug or placebo in a double-blind randomized controlled trial. The study observed 83 participants for 8 days. No statistically significant reduction in pain was determined.[14]

Botulinum Toxin

Another treatment modality involves botulinum toxin. Botulinum toxin is considered an invasive pharmacologic intervention (Fig. 2). Studies suggest that botulinum toxin injection may be highly successful in cases that have failed pharmacologic therapy.[15,16]

The primary target of botulinum toxin injection is the group of muscles of mastication, including the temporal, masseter, and lateral pterygoid muscles. In those who have failed conventional treatment, botulinum toxin may improve symptoms. There are reports of pain relief up to 90% in patients with muscular-type temporomandibular pain.[17,18]

Botulinum toxin is produced by the bacteria *Clostridium botulinum*. Various toxins are available, referred to as botulinum toxin A, botulinum toxin B, and so on through G. Botulinum toxin A is the most common form used in the treatment of temporomandibular disorder and other facial indications, and is known by the trademark Botox.

Good results have been shown when botulinum toxin is used for the treatment of habitual dislocation of the TMJ.

The mechanism of action of botulinum toxin is inhibition of the release of acetylcholine at the neuromuscular junction.[18-20] The toxin binds and is then internalized at nerve terminals. Once internalized, it is released into the cytoplasm and a complex of botulinum toxin and neural proteins is formed.

This complex then causes proteolysis of a synaptosomal-associated protein called SNAP-25. SNAP-25 is required for synaptic vesicles containing acetylcholine to fuse at the nerve terminal membrane. This reaction results in inhibition of the normal exocytosis of acetylcholine.[21,22] Decreased amounts of acetylcholine at the motor end plate leads to decreased amounts of receptors and neural activity and finally muscular denervation.

Clinical effects become apparent within 1 to 2 days. The result is temporary. Over a time span of 3 to 18 months, the targeted muscles form new acetylcholine receptors resulting in the eventual return of normal muscular function.[22-24]

Good results have been shown when botulinum toxin is used for the treatment of habitual dislocation of the TMJ.[25] It has also been suggested that botulinum toxin should be considered as first-line therapy in those of advanced age. It has been recommended as the first line of therapy for those with neurologic or systemic disease. Beneficial effects of pain reduction have been reported to last an average of 3 to 6 months.[26]

A study including only 5 patients with habitual dislocation to whom 25 to 50 units/muscle of botulinum toxin was used at 2 sites into the lateral pterygoid muscles showed no recurrences of dislocation and no further injections were necessary.[27]

Another small study that included 4 cases of recurrent TMJ dislocation with neurogenic origins showed tremendous improvement after botulinum toxin A administration. Participants were locally infiltrated with botulinum toxin A at the level of the external pterygoid muscles bilaterally using palpation and an electrical amplifier for muscle identification. Between 10 and 25 units of botulinum toxin A were used. Only minor transient adverse effects were reported.[28]

A comprehensive review analyzed a few randomized controlled trials of botulinum toxin A therapeutic application in the treatment of orofacial pain and cervical dystonias.[29] The purpose of this study was to show that botulinum toxin is safe and effective in the treatment of maxillofacial conditions before dental implantation. Results for chronic facial pain were shown in 1 randomized controlled trial including 90 participants divided into 2 groups; 1 with normal saline as the injectate and the other with botulinum toxin A injected into the masticatory muscles. Participants were evaluated 4 weeks after therapy, and decreased facial pain was reported in 91% of the participants. Only mild and transient adverse effects were seen. The visual analog scale was used for pain assessment.

Another major study included 26 participants before and after botulinum toxin injection. It revealed a significant difference between preinjection and postinjection pain scores[30] and

demonstrated statistically significant differences in subjective headaches, functional dysfunction, and mouth opening. Participants were observed for 3 months at 2-week intervals. Electromyographic guidance was used for accurate needle placement into the lateral pterygoid muscle bilaterally, which was injected with 12.5 units of botulinum toxin A. The medial pterygoid muscle, under electromyographic guidance, was injected with 12.5 units bilaterally. Injections of the temporalis and masseter muscles were performed percutaneously without electromyographic guidance with 25 units of botulinum toxin bilaterally. Increased pain was reported by all participants on the first day postinjection. Complete absence of pain was reported in 8 patients, and partial relief of pain was reported in the remaining participants with 1 exception. This patient reported an increase in symptoms postinjection. Two patients failed to have increased functional range of motion. One patient developed a temporary dysphonia and dysphagia postinjection that later resolved.

Complications of botulinum toxin include pain at the site of injection, temporary injection-site swelling, muscular weakness, transient numbness, transient headache, nausea, flu-like symptoms, bruising at the site of injection, erythema, and development of tolerance.[31-33]

Conclusion

Reviewing the treatment modalities for temporomandibular disorder, it seems that no single therapy has been shown to be successful. Rather, the correct etiology is necessary to establish appropriate management. Treatment modalities are highly variable and should be chosen on the basis of the primary cause of dysfunction, which itself is not always clear. Invasive procedures should be limited to those cases in which a clear etiology can be demonstrated that is amenable to surgical correction. Conservative management that includes behavioral therapy, psychotherapy, and physiotherapy should be the first line in those individuals with clear emotional and psychologic issues. It has been well documented that stress and psychologic factors play a role in some patient populations, and the main therapeutic focus in these cases should be behavioral modification and relaxation techniques. Botulinum toxin injection has been shown to be successful in many cases of pain, but results are usually not permanent.

Acknowledgment

This article was reviewed by Elizabeth A.M. Frost, MD, Professor of Anesthesiology, Mount Sinai School of Medicine, New York, New York. ■

References

1. Moore KL, Dalley AF. *Clinically Oriented Anatomy*. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2009;923-927.

2. Okeson JP, de Leeuw R. Differential diagnosis of temporomandibular disorders and other orofacial pain disorders. *Dent Clin N Am*. 2011;55:105-120.

3. Leopard PJ. Surgery of the non-ankylosed temporomandibular joint. *Br J Oral Maxillofac Surg*. 1987;25:138-148.

4. Bonica J, Truelove EL, Dworkin SF, et al. *Facial Head Pain Caused by Myofascial Temporomandibular Disorders in Bonica's Management of Pain*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001:895-902.

5. Harkins S, Linford J, Chen J, et al. Administration of clonazepam in the treatment of TMD and associated myofascial pain: a double-blind pilot study. *J Craniomandib Disord*. 1991;5(3):179-186.

6. Kimos P, Biggs C, Mah J, et al. Analgesic action of gabapentin on chronic pain in the masticatory muscles: randomized control trial. *Pain*. 2007;127:151-160.

7. Winocur E, Gavish A, Halachmi M, et al. Topical application of capsaicin for the treatment of localized pain in the TMJ area. *J Orofac Pain*. 2000;14(1):31-36.

8. Ekberg E, Kopp S, Akerman S. Diclofenac sodium as an alternative treatment of temporomandibular joint pain. *Acta Odontol Scand*. 1996;54(3):154-159.

9. Ta Le, Dionne RA. Treatment of painful temporomandibular joints with a cyclooxygenase-2 inhibitor: a randomized placebo-controlled comparison of celecoxib to naproxen. *Pain*. 2004;111:13-21.

10. Lobo S, Mehta N, Forgione AG, et al. Use of Theraflex-TMJ topical cream for the treatment of temporomandibular joint and muscle pain. *Cranio*. 2004;22(2):137-144.

11. Herman CR, Schiffman EL, Look JO, et al. The effectiveness of adding pharmacologic treatment with clonazepam or cyclobenzaprine to patient education and self-care for the treatment of jaw pain upon awakening: a randomized clinical trail. *J Orofac Pain*. 2002;16(1):64-70.

12. Nguyen P, Mohamed SE, Gardiner D, et al. A randomized double blind clinical trial of the effect of chondroitin sulfate and glucosamine hydrochloride on temporomandibular joint disorder: a pilot study. *Cranio*. 2001;19:130-139.

13. Roldan OV, Maglione H, Carreira R, et al. Piroxicam, diazepam, and placebo in the treatment of temporomandibular joint dysfunction. Double blind study [in Spanish]. *Rev Asoc Odontol Argent*. 1990;78(2):83-85.

14. Rossi E, Gallardo F, Weil MW. Prazepam as the initial treatment of myofascial pain-dysfunction syndrome. *IRCS Medical Science*. 1983;11:637-638.

15. Schwartz M, Freund B. Treatment of temporomandibular disorder with botulinum toxin. *Can Clin J Pain*. 2002;18:S198-S203.

16. Stefan KA, Ihde DMD, Vitomir SK. The therapeutic use of botulinum toxin in cervical and maxillofacial conditions: an evidence-based review. *Oral Surg Oral Med Oral Pathol Oral Radiol Emdod*. 2007;104:e1-e11.

17. Fuster-Torres MA, Berini-Aytés L, Gay-Escoda C. Salivary gland application of botulinum toxin for the treatment of sialorrhea. *Med Oral Patol Oral Cir Bucal.* 2007;12(7):E511-E517.

18. Monroy PG. The use of botulinum toxin A in the treatment of severe bruxism in a patient with autism: a case report. *Spec Care Dentistry*. 2006;26(1):37-39.

19. See SJ, Tan EK. Severe amphethamine-induced bruxism: treatment with botulinum toxin. *Acta Neurol Scand.* 2003;107(2):161-163.

20. Frei K, Truong DD, Dressler D. Botulinum toxin therapy of hemifacial spasm: comparing different therapeutic preparations. *Eur J Neurol*. 2006;13(s1):30-35.

21. Kim HJ, Yum KW, Lee SS, et al. Effects of botulinum toxin type A on bilateral masseteric hypertrophy evaluated with computed tomographic measurement. *Dermatol Surg.* 2003;29(5):484-489.

22. Song PC, Schwartz J, Blitzer A. The emerging role of botulinum toxin in the treatment of temporomandibular disorders. *Oral Dis.* 2007;13(3):253-260.

23. Benedetto AV. Asymmetrical smiles corrected by botulinum toxin serotype A. *Am Soc Dermatol Surg*. 2007;33(s1):S32-S36.

24. Lai AT-Y, Chow T-L, Kwok SP-Y. Management of salivary fistula with botulinum toxin type A. *Ann Coll Surg Hong Kong*. 2001;5(4):156-157.

25. Bhidayasiri R, Cardoso F, Truong DD. Botulinum toxin in blepharospasm and oro- mandibular dystonia: comparing different botulinum toxin preparations. *Eur J Neurol*. 2006;13(s1):21-29.

26. Ugboko VI, Oginni FO, Ajike SO, et al. A survey of temporomandibular joint dislocation: aetiology, demographics, risk factors, and management in 96 Nigerian cases. *Int J Oral Maxillofac Surg*. 2005;34:499-502.

27. McKelvey LE. Sclerosing solution in the treatment of chronic subluxation of the temporomandibular joint. *J Oral Surg (Chic)*. 1950;8:225-236.

28. Moore AP, Wood GD. Medical treatment of recurrent temporomandibular joint dislocation using botulinum toxin A. *Br Dent J*. 1997;183:415-417.

29. Martínez-Pérez D, García Ruiz-Espiga P. Recurrent temporomandibular joint dislocation treated with botulinum toxin: report of 3 cases. *J Oral Maxillofac Surg*. 2004;62:244-246.

30. Mujakperuo HR, Watson M, Morrison R, et al. Pharmacological interventions for pain patients with temporomandibular disorders. *Cochrane Database Syst Rev*. 2010;(10): CD004715. doi: 10.1002/14651858.CD004715.pub2.

31. Daelen B, Thorwirth V, Koch A. Neurogenic temporomandibular joint dislocation. Definition and therapy with botulinum toxin [in German]. *Nervenarzt*. 1997;68:346-350.

32. Merrill RG. Habitual subluxation and recurrent dislocation in a patient with Parkinson's disease: report of case. *J Oral Surg*. 1968;26:473-477.

33. Aquilina P, Vickers R, McKellar G. Reduction of a chronic bilateral temporomandibular joint dislocation with intermaxillary fixation and botulinum toxin A. *Br J Oral Maxillofac Surg*. 2004;42: 272-273.

Conversation: Richard B. Lipton, MD, on the Impact of Nausea in Migraine and Tailoring Treatment to the Attack, and to the Patient

Richard B. Lipton, MD

New data illuminate the impact of nausea on migraineurs, indicating that presence of the cosymptom leads to a greater disease burden. And in many cases, the nausea is getting in the way of pain relief, according to investigators who presented new data from a landmark longitudinal study sponsored by the National Headache Foundation at the American Headache Society annual scientific meeting in June 2011.

"Recognizing nausea may be a key to reducing the overall burden of migraine for certain episodic migraine sufferers," said Richard B. Lipton, MD, professor and vice chair of the Saul R. Korey Department of Neurology at the Albert Einstein College of Medicine, and director of the Montefiore Headache Unit in New York, New York.

Lipton is lead investigator of the American Migraine Prevalence and Prevention (AMPP) Study, based on data compiled from 2004 through 2009 examining nearly 163,000 Americans age 12 years and older selected to be representative of the US population. On the basis of a validated questionnaire, the researchers reviewed headache symptoms and frequency, impairment, current use or past use of migraine prevention medications (whether prescribed or over-the-counter), and use of medications prescribed for other indications but known to prevent migraine headaches (coincident use).

The findings showed that patients who reported frequently experiencing nausea with migraine were more likely to be disabled by the disease and more likely to be dissatisfied with their treatment.

They also had greater odds of experiencing other symptoms, including the following:

- One-sided pain;
- Throbbing or pulsating pain;
- Sensitivity to light, sound, and/or smell;

- Loss of appetite;
- Neck pain; and
- Sinus pain.

In an interview with *Topics in Pain Management* (*TPM*), Lipton elaborated on the study and what clinicians can do to make sure patients can get the best chance of relief, from the range of medications.

TPM: Can you tell us more about the AMPP study?

Lipton: Our investigation is a 5-year longitudinal study of a large representative sample of the US population looking mostly at migraine headaches but also other headaches and pain disorders.

By way of background, in 2004 we recruited the sample by mailing questionnaires to 120,000 US households. We got 163,000 respondents, about 28,000 of whom have severe headaches. We followed a random sample of 24,000 people who have severe headaches in 2004 with annual questionnaires looking at headache features of the pain, patterns of treatment, disease burden, and so forth.

The study has been a collaboration between the National Headache Foundation, which has very generously funded this study since 2004, and Albert Einstein College of Medicine.

TPM: What was the new analysis of data you presented to the scientific meeting this spring?

Lipton: The findings we presented at the American Headache Society (in June) were on the relationship between migraine and nausea. And, of course, the fact that migraine patients get nausea is well known to neurologists and pain specialists because migraine is often known as "sick" headaches, and nausea is one of the features that are cardinal symptoms and part of the definition of a migraine.

What was new in this study was that migraine sufferers who had nausea were more likely to be disabled by their headaches, more likely to miss work, more likely to miss school, more likely to have a greater family impact, more likely to go to the emergency room, and less likely to be satisfied with their usual medication.

Migraine sufferers who had nausea were more likely to be disabled by their headaches… and less likely to be satisfied with their usual medication.

So the picture that emerges is that if you meet the case definitions for migraines, and if you have typical migraine pain with nausea or typical migraine pain with sensitivity to light or sound, the patient with nausea was more likely to be disabled and more likely to be dissatisfied with treatment.

TPM: Why is it that the migraine sufferers with nausea are more severely disabled and dissatisfied with treatment, and why is nausea such a common feature in migraine?

Lipton: There is evidence from previous studies that with migraine, the pain likely comes from inflammation and dilation of meningeal blood vessels, that pain is carried by the trigeminal nerve to a structure called the trigeminocervical complex or the trigeminal nucleus caudalis, which is the brain stem extension of the dorsal horn of the spinal cord.

So it turns out that in animal models of migraine, the best one is where the sagittal sinuses are stimulated so that you can show activation in the trigeminocervical complex, and you also show activation in a structure called the nucleus tractus solitarius (NTS). And that nucleus is a major emesis-dominating center in the brain. So we think what happens is with activation of the pain pathway, comes nausea as well. The more intense the activation of pain, the more the chance the patient will be nauseated.

So the timing isn't perfect in the sense that sometimes the nausea can precede the pain or outlast the pain. We think pain drives nausea in people with migraine, and that as part of that, migraine sufferers develop gastric paresis, which is to say the digestive system becomes somewhat paralyzed.

TPM: And that gastric paralysis keeps them from absorbing the medication for pain?

Lipton: We know that medicine works best in migraine if you take it early. Some people who are particularly prone to develop nausea say they will take the medicine and vomit 6 hours later, and the pills are still in their stomach, which is a sign of gastric paresis.

So we think that part of the reason that migraine sufferers with nausea have more severe disease, is that nausea is a consequence of severe pain. Part of the reason migraine sufferers with nausea are less satisfied with their treatment is that they don't absorb it if they're nauseated.

So in migraine sufferers who have trouble with nausea, treatment strategy should be developed in a way that takes nausea into account.

TPM: How should clinicians take nausea into account when tailoring a treatment plan?

Lipton: There are a bunch of ways of doing that. One way is to actually give medicines that treat nausea as well as pain. Another strategy is to give medications that don't depend on the digestive system for absorption.

Traditionally, we've done that primarily with injectibles or nasal sprays. The 2 new approaches that are emerging were old medicines with new tricks—new routes of administration. One is a sumatriptan patch (Zelrix, NuPathe Inc.), where the patient applies an iontophoretic patch, so that electricity drives the medicine across the skin. The other related approach is an old medicine, dihydroergotamine,

Why Wasn't Nausea Being Treated?


Robert R. Dalton

Nausea is such a common symptom of migraine that it seems ironic it would go untreated in so many cases. So how does that happen?

"There are a couple of answers to that," said Robert Dalton, executive director of the Chicago-based National Headache Foundation. "One is that historically there is a lot of communication breakdown that happens between patients and clinicians when it comes to migraine."

It starts with patients trying to find a pattern to their attacks.

"Very often there is a tendency to assume that because something isn't consistent, that it isn't related," Dalton said. "So the patient who's getting nauseated every second or third time they have a migraine may be setting that aside as unrelated.

"And a lot of times, it's because the question wasn't getting asked, "he said. "The patient says, I have this terrible terrible headache, and a determination is made that it's a migraine. Even the ones who come up with a good treatment regimen don't always look into the other side effects and impact of them."

Dalton said reimbursement and drug costs may also play a role.

"For example, the triptans are great medications in the oral form and they are often generic and inexpensive. There may be a tendency to see if that's an adequate solution. If the patient takes it early enough that they don't get to the nausea stage," Dalton said.

"But there are cases where a migraine attack does not always come with advance warning. And once the nausea takes hold, then the oral medication is no longer a viable solution," he said. "So having other alternatives, like the injectibles, patches, inhalants—there are multiple variations out there—is necessary. That may add cost but, as the study shows, it can also greatly decrease the negative impact of migraine."

Dalton said the data on the impact of nausea can help more people understand migraine as a disease.

"It's important to make it clear that people—health care professionals, migraineurs, general population—often do not realize that migraine is so much more than just a headache," Dalton said. "By making them aware that nausea is often a co-symptom with headache and is part of the disease, this has a certain value just in terms of better understanding, so people are more often treated and properly diagnosed."

Data indicate that only half of the people with migraine in this country have an actual diagnosis.

"A common circumstance is somebody with migraine, especially if they haven't moved into the chronic phase, is going to the doctor and talking about headache in the context of everything else going on in their lives, and being told it's stress or it's fatigue, something you ate, something else in the environment, and not being treated as a migraine," Dalton said. "Nausea, if not understood as a common symptom of migraine, can then cause the health care provider to assume the headache was a co-symptom of the flu or secondary to some other disease," he said.

Even with a diagnosis, many patients still aren't getting the relief they could.

"The belief is that less than half of the people with the diagnosis are being properly treated," he said.

that has been developed as an inhaler, similar to the nasal spray, but the advantage is the absorption surface area of the lung is much larger (Levadex, in phase 3 development by MAP Pharmaceuticals).

There are also Compazine suppositories that help with the pain and nausea. But patients don't like suppositories very much in North America.

TPM: Do patients in other countries like suppositories for migraine?

Lipton: The French like suppositories. I certainly use them in my practice for patients who are open to considering them as a possibility when they can't absorb oral medications.

Part of assessing the patient with headache is asking about nausea and making a determination whether treatment for nausea in addition to treatment for pain is necessary, or if a treatment that doesn't depend on the digestive system is necessary.

TPM: If the pain is addressed through medication, does that usually also treat the nausea? If the pain is under control, does that prevent the nausea from coming on?

Lipton: Yes. That's what the clinical trials show. In addition to the drugs that are commonly used to treat a broad range of disorders and migraine-specific medications, we find that with the migraine-specific medications, when they relieve pain, they also relieve nausea. And I think that's in part because the pain drives the nausea physiologically in the brain stem. So if you get rid of the pain, you get rid of the nausea.

TPM: So it can be done if you plan ahead for the nausea and what to do if it comes on. Is it a matter of strategy and communication with the patient about what to do and when to do it?

Lipton: With some patients, if you catch the headache early, oral medication may well be effective. If you don't catch the headache early and nausea and gastric paresis develops, it may be too late to use oral medication, and at that point you may need to get the drug in through a different route.

Then, there are some patients who may not develop nausea, and the oral medication may work for a much longer period.

So the message is really that acute treatment works best if you tailor it to the patient, but also to the attack.

TPM: Tailor the treatment to the attack?

Lipton: By that I mean to the timing of when you catch the attack. For example, some patients, if they catch the attack during the day and take their oral medication, they can do just fine, whereas another time, that same patient might wake up in the morning with a severe migraine and nausea, if the migraine evolved while they were asleep and they missed that treatment window.

TPM: Is there anything else you wish to highlight?

Lipton: In the subgroup of people with episodic migraines, they sometimes evolve into chronic headaches—which means 15 or more headaches a month.

Pain conditions sometimes undergo a transition from episodic to chronic pain. It's an issue of import for doctors treating migraines.

We've learned a lot about risk factors for migraine progression of the disease, which include high headache frequency, nausea, comorbid depression, and allodynia with the migraine attack. So part of the treatment strategy for people with episodic migraine is to reduce the chance of the disease progressing.

There has never been a study showing that treatment prevents the progression from episodic to chronic pain, but there

Continued on page 12

Mitochondrial Damage Associated With HIV-Related Sensory Neuropathy

By Sonia Elabd, MA

In patients with HIV, sensory neuropathy is one of the most common complications. A study published in the January 2011 issue of *Annals of Neurology* posits that the reason for the neuropathy is the accumulation of damaged mitochondrial DNA (mtDNA) in the distal nerves of these patients.[1]

"For the first time we have a hypothesis backed by human data to explain why the distal ends of long nerves are susceptible to degeneration in peripheral neuropathies," said Ahmet Höke, MD, PhD, principal author of the study and professor of neurology and neuroscience, and director of the Neuromuscular Division at Johns Hopkins University.

"We linked two epidemiological observations—ie, older and taller people have peripheral neuropathy more commonly—to a testable hypothesis about mitochondria's role in axons," Höke said. "Although we gathered the supporting data in HIV patients, I believe the same applies to diabetic and other types of peripheral neuropathies."

The study examined postmortem tissue samples from dorsal root ganglia and sciatic nerves and sural nerves from 11 patients with HIV-associated sensory neuropathy, 13 patients with HIV but without sensory neuropathy, and 11 HIV-negative patients, who were used as a control. The authors documented some interesting results.

"Consistent with the idea that in peripheral nerve fibers, axons are the largest consumer of mitochondria-derived ATP, we found that in humans and primates, the vast majority of mitochondria (~84% in humans and ~93% in primates) were located within unmyelinated and myelinated axons, whereas Schwann cells and other cells harbored only a small percentage of all nerve fiber mitochondria,"[1] wrote Höke.

Amounts of mitochondrial common deletion mutations were greater in sural nerve specimens of patients with HIV and sensory neuropathy (SN) than in those with HIV and with no neuropathy.

"Our findings suggest that mtDNA damage accumulates in distal mitochondria of long axons, especially in patients with HIV-SN, and that this may lead to reduced mitochondrial function in distal nerves relative to proximal segments. Although our findings are based on HIV-SN, if confirmed in other neuropathies, these observations could explain the length-dependent nature of most axonal peripheral neuropathies," wrote Höke.

The researchers suggest that these findings could be applied to develop agents that target mitochondrial function.

"For example, one can develop an assay to screen for drugs that improve mitochondrial function or prevent mtDNA deletions/mutations. There are drug companies and groups developing and testing drugs that enhance mitochondrial function because impaired mitochondrial function may be a common mechanism for many neurodegenerative disorders," said Höke. ■

Reference

1. Lehmann HC, Chen W, Borzan J, et al. Mitochondrial dysfunction in distal axons contributes to human immunodeficiency virus sensory neuropathy. *Ann Neurol*. 2011;69:100-110.

Topics in Pain Management CME Quiz

To earn CME credit, you must read the CME article and complete the quiz and evaluation assessment survey on the enclosed form, answering at least 70% of the quiz questions correctly. **Select the best answer and use a blue or black pen to completely fill in the corresponding box on the enclosed answer form.** Please indicate any name and address changes directly on the answer form. If your name and address do not appear on the answer form, please print that information in the blank space at the top left of the page. Make a photocopy of the completed answer form for your own files and mail the original answer form in the enclosed postage-paid business reply envelope. Your answer form must be received by Lippincott CME Institute by **July 31, 2012.** Only two entries will be considered for credit.

Online quiz instructions: To take the quiz online, go to *http://cme.LWWnewsletters.com*, and enter your *username* and *password*. Your *username* will be the letters LWW (case sensitive) followed by the 12-digit account number above your name on the paper answer form mailed with your issue. Your *password* will be 1234; this password *may not* be changed. Follow the instructions on the site. You may print your official certificate *immediately*. Please note: Lippincott CME Institute, Inc. *will not* mail certificates to online participants. **Online quizzes expire at 11:59 pm Pacific Standard Time on the due date.**

1. **The most common origin of orofacial pain is**
   A. the muscles of mastication
   B. the TMJ
   C. inflammation of the facial nerve
   D. none of the above

2. **Which of the following statements to describe the TMJ is/are *true*?**
   A. It connects the mandible to the skull.
   B. It is a modified hinge-type synovial joint.
   C. It contains 2 synovial membranes.
   D. All of the above

3. **Which one of the following statements describing the action of the muscles of mastication is *true*?**
   A. The masseter opens the mouth.
   B. The temporal and medial pterygoid muscles elevate the mandible and close the mouth.
   C. Retrusion of the lower jaw is produced by the lateral pterygoid and masseter muscles.
   D. Innervation is from the facial nerve.

4. **Temporomandibular disorder**
   A. mainly affects young men who grind their teeth
   B. typically occurs in the second decade of life
   C. may be considered chronic if pain persists for 1 month
   D. usually causes the sufferer to seek medical help within 1 month of symptoms

5. **Typical symptoms of temporomandibular disorder include**
   A. periauricular pain
   B. tinnitus
   C. clicking of the jaw
   D. all of the above

6. **Etiologies of temporomandibular disorder include**
   A. excessive swallowing
   B. excessive chewing
   C. muscle spasms
   D. all of the above

7. **Which one of the following populations has the highest prevalence of temporomandibular disorder?**
   A. Women in the third and fourth decades
   B. Women older than 60
   C. Men in the third and fourth decades
   D. Men older than 60

8. **Which one of the following drugs is most effective for treatment of temporomandibular disorder?**
   A. Clonazepam
   B. Gabapentin
   C. Topical capsaicin
   D. Celecoxib

9. **Botulinum toxin action is explained by**
   A. inhibition of acetylcholine release
   B. stimulation of acetylcholine secretion
   C. inhibition of epinephrine release
   D. stimulation of acetylcholine reuptake

10. **Complications associated with the use of botulinum toxin include**
    A. pain
    B. swelling
    C. muscle weakness
    D. all of the above

Continued from page 10

are a lot of remedial risk factors. If nausea is a risk factor, maybe treating early might prevent against progression.

It may be that treating early might prevent against progression, but the issue is that reducing attack frequency is clearly beneficial today, for patients.

TPM: What are the main messages you want to emphasize for clinicians?

Lipton: Nausea is a very common symptom that probably arises as a response to pain through known anatomy.

Our data demonstrate that nausea is very common migraine—80% of migraine sufferers have nausea some of the time, and half have nausea with at least half their attacks.

It's important for doctors to assess it so they can either offer treatments that address the nausea or they have treatments that can circumvent the gut and still get into the bloodstream. ■

NEWS IN BRIEF

Who Was That Unmasked Doctor? Meningitis Cases Linked to Specific Physicians And Spinal Injections

The Centers for Disease Control and Prevention (CDC) issued a clinical reminder to physicians and other health care providers to always wear facemasks for cases that involve injecting any material into the spine or inserting a catheter.

The reminder was issued after specific cases of meningitis were linked to physicians who did not wear a mask when performing these procedures. It is believed that oral flora from the providers was transmitted by droplets and infected the patients.

The CDC "is concerned about the occurrence of bacterial meningitis among patients undergoing spinal injection procedures that require injection of material or insertion of a catheter into epidural or subdural spaces (e.g., myelogram, administration of spinal or epidural anesthesia, or intrathecal chemotherapy)," the reminder reads.

"Outbreaks of bacterial meningitis following these spinal injection procedures continue to be identified among patients whose procedures were performed by a healthcare provider who did not wear a facemask (eg, may be labeled as surgical, medical procedure, or isolation mask), with the most recent occurrence in October 2010 (CDC, unpublished data). This notice serves as a reminder that facemasks should always be worn by healthcare providers when performing these spinal injection procedures."

This is not the first time the CDC has investigated multiple outbreaks of bacterial meningitis among patients undergoing spinal injection procedures. Recent outbreaks have occurred among patients in acute-care hospitals who received spinal or epidural anesthesia, and also among patients at an outpatient imaging facility who underwent myelography.

In each of these outbreak investigations, nearly all spinal injection procedures that resulted in infection were performed by a common health care provider who did not wear a facemask. The strain of bacteria that was isolated from the cerebrospinal fluid of these patients was identical to the strain recovered from the oral flora of the health care provider who performed the spinal injection procedure. These findings illustrate the risk of bacterial meningitis associated with droplet transmission of the oral flora from health care providers to patients during spinal injection procedures.

Facemasks have been shown to limit spread of droplets arising from the oral flora, according to the CDC.

In addition to reminding them to wear a facemask, the CDC also reminded health care providers to ensure adherence to all CDC-recommended safe injection practices including using a single-dose vial of medication for only 1 patient.

The CDC further emphasized that these recommendations apply not only in acute-care settings such as hospitals, but in any setting where spinal injection procedures are performed, such as outpatient imaging facilities, ambulatory surgery centers, and pain management clinics. (See Centers for Disease Control and Prevention. CDC Clinical Reminder: Spinal Injection Procedures Performed without a Facemask Pose Risk for Bacterial Meningitis. http://www.cdc.gov/injectionsafety/PDF/Clinical_Reminder_Spinal-Infection_Meningitis.pdf.) ■

Coming Soon:

- Onsolis: The Future of Opiate Prescribing Under Risk Evaluation and Mitigation Strategies (REMS)