Tender GC, Walbridge S, Olah Z, et al. Selective ablation of nociceptive neurons for elimination of hyperalgesia and neurogenic inflammation. J Neurosurg 2005;102:522–525.

Articles that were published more than 3 years ago are not frequently reviewed in this journal, but I think this fascinating study deserves to be highlighted here. The authors conducted a simple yet elegant experimental study of selective ablation of nociceptive neurons that produced very clear outcomes. Using a compound called RTX, which is an agonist to the vanilloid receptor 1 (VR1), they hoped to destroy VR1-positive neurons (nociceptors) while not adversely affecting other neurons in the trigeminal ganglion. This compound was infused directly into the right ganglion of 3 rhesus monkeys while 1 monkey was injected with vehicle only. Sensory behavioral testing was conducted at 1, 4, and 7 weeks postinfusion. After sacrifice at 12 weeks, histologic and immunohistochemical analyses were performed.

Sensory testing revealed normal responses to tactile stimulation on both the treated and untreated sides. There was a dramatic reduction in blinking on the treated side following corneal application of capsaicin to both eyes, which means that hyperalgesia was practically eliminated on that side. Clinical evaluation indicated normal feeding and other motor activities continuing throughout the study period, implying that motor neurons were not affected. Just prior to sacrifice, each animal had capsaicin applied to the face and scalp. Within 10 minutes, this produced reddening of the entire face and scalp in the untreated animals (a response mediated by the release of neurotransmitters and other inflammatory mediators from adjacent tissues), while the treated animals had a clear hemifacial difference in reddening response. Gross and histologic findings were: no keratitis or abrasion of capsaicin-treated corneas; oral mucosa showed no signs of injury; preservation of normal architecture in the RTX-treated ganglia; and absence of nonspecific toxicity effects. Immunohistochemical analysis showed uniform ablation of the VR1-positive neurons in the treated ganglia.

In the Discussion, the authors state that both C fibers and Type 2 A-delta neurons express VR1, and it appears that the infusion of RTX is capable of selectively ablating these neurons without affecting the functions of A-beta and Type 1 A-delta fibers. This is evidenced by the elimination of hyperalgesia, neurogenic inflammation, and cellular mediators of neuropathic pain on the treated side. Therefore, these results imply a possible new direction for the development of "new site-specific, physiological-based treatment for pain syndromes, including trigeminal neuralgia." Subsequent papers published by these and other authors have confirmed these preliminary findings, but the development of a clinically useful version of this approach may not occur in the near future. *(CSG)*

Sun W, Dong L, Kaneyama K, Takegami T, Segami N. Bacterial diversity in synovial fluids of patients with TMD determined by cloning and sequencing analysis of the 16S ribosomal RNA gene. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008;105:566-571.

This paper reports the results of a study of bacterial presence in the synovial fluid of 27 patients with TMD diagnoses of nonreducing disc displacement (25/27) and/or osteoarthritis (7/27); 1 patient had fluid drawn from both joints, so there were 28 samples to analyze. The primary method for examining these samples has been reported before, namely, polymerase chain reaction (PCR). However, these authors utilized a more sophisticated method involving specially designed PCR primers and subsequent cloning and sequencing of the PCR products. Then the 16S ribosomal RNA gene sequences could be compared against those from a wide variety of known bacterial species. As a result, they were able to identify 11 bacterial species, some of which were previously hard to find because they were fastidious or uncultivatible. A group of 5 patients who had temporomandibular joint (TMJ) dislocation problems but no pain or inflammation were used as controls.

The results of this assay were positive for 19 of 28 joints, with 4 bacterial species showing up in at least 4 joints, while the other 7 species were found in only 1 or 2 joints. There were no positive findings in the 5 control joints. Eight patients had mixed strains of bacteria, while the other 11 had only 1 species present. No significant association was found with any clinical parameters such as gender, TMJ pain, magnetic resonance imaging (MRI) findings, or limited opening. No chlamydia or Mycoplasma organisms were found, which contradicts some previous reports (some of which have been criticized for possible cross-contamination); these authors make a point of the absolute sterility and control of their collection and assessment procedures.

The discussion of these data does not make it clear whether these discovered bacteria should be regarded as pathogens for TMJ conditions or as opportunists that find their way into inflamed joints. The authors cite some relevant studies from the general orthopedic literature, and they seem to lean in the direction of calling them pathogens—but then they state that perhaps multiple bacteria must be present to contribute to pathogenesis. Future studies will be required to answer these questions, but for now these findings should be of interest to both scientists and practitioners. *(CSG)*

Lewis MAO, Sankar V, De Laat A, Benoliel R. Management of neuropathic orofacial pain. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007; 103 (suppl 1): S32-S38.

This excellent review comes from the Fourth World Workshop on Oral Medicine, in which selected experts reviewed the literature on a variety of oral medicine topics. This group focused primarily on trigeminal neuralgia, postherpetic neuralgia, and traumatic trigeminal neuropathies. They reviewed literature from 1986 through 2006, and in a large table they summarize the findings from 29 controlled clinical trials. The objective was to determine which (if any) systemic, topical, or other therapies are efficient in management of patients with orofacial pain. The last category included alternative or complementary therapies as well as surgical procedures, and their findings for these modalities appear only in the online version of the article.

The results are presented first in brief summaries for each of the 3 clinical conditions which highlight the major conclusions. Then each category of systemic drugs (anticonvulsants, antidepressants, opioids, and others) as well as each category of topical medications (antidepressants, aspirin, capsaicin, and anesthetics) is discussed separately. For trigeminal neuralgia, carbamazepine remains the drug of choice, but both oxcarbazepine and gabapentin have been found to be helpful in refractory cases. This condition (unlike the other 2) is treatable by certain surgical procedures when indicated, and these are discussed in the online version. For postherpetic neuralgia, an important finding was that early use of antiviral drugs in herpes zoster cases reduces the incidence of this painful disorder. For treatment, positive results have been obtained with tricyclic antidepressants, gabapentin, pregabelin, opioids, and topical lidocaine patches. Unfortunately, no randomized clinical trials have been done to investigate pharmacotherapy for traumatic trigeminal neuropathies, so clinicians have to base their decisions on the literature for spinal injuries or other neuropathic

pain conditions. It appears that the tricyclic antidepressants and gabapentin (or combinations of both) are the most likely to be helpful; opioids may be effective, and mexiletene has been shown to be effective for some traumatic neuropathies.

The printed version of this article has 70 references, but the online version has 248. In that version there are broader definitions of terms as well as some discussion of other approaches, including transcutaneous electrical nerve stimulation, tryptophan, low-power lasers, and intranasal cocaine. Under the heading of complementary and alternative approaches, positive findings have been reported for biofeedback, acupuncture, and relaxation therapies, but none for a variety of other popular concepts in that domain. Finally, there is a good summary of the data on rhizotomy, ablative peripheral procedures, microvascular decompression, and the gamma knife, all of which have been shown to have some value in the treatment of trigeminal neuralgia.

The authors conclude that there is a great need for further research into both the mechanisms and the management of these painful conditions. *(CSG)*

Rompré PH, Daigle-Landry D, Guitard F, Montplaisir JY, Lavigne GJ. Identification of a sleep bruxism subgroup with a higher risk of pain. J Dent Res 2007;86:837–842.

This paper is one of a continuing series coming from this well-known Montreal group. It features a retrospective look at the data collected from 100 people over 15 years who initially were identified as sleep bruxers based on a positive home history of nocturnal tooth grinding. During the same period 43 people were selected as control subjects, and they underwent the same sleep laboratory studies as the so-called bruxers. In 1996 Lavigne et al had published criteria for establishing a sleep lab diagnosis of sleep bruxism (SB-RDC), based on polygraphic studies of oral motor activities during sleep in 18 bruxers and 18 controls. These criteria were: > 4 sleep bruxism episodes per hour of sleep; >25 sleep bruxism bursts per hour of sleep; and > 1 sleep bruxism episode with tooth-grinding noises. This paper uses this larger data set to validate these criteria, while also looking at the relationship between bruxism and pain. It has been hypothesized that pain in bruxers is associated with *lower* frequencies of orofacial motor activities, which seems counterintuitive, but the findings from this study confirm that association.

Using the SB-RDC, 54 of the 100 bruxers (ie, home history of bruxism) were either in a high or moderate cluster, which put them in the category of true sleep bruxers, and therefore suitable for further sleep laboratory studies of various associated phenomena. Eight of the 43 controls ended up in a high cluster, which rendered them unsuitable for further control studies, and in fact these individuals showed more episodes per hour than excluded bruxers ($P < .05$). The most significant finding was that the 46 excluded bruxers were nearly 4 times more likely "to complain of painful jaw on awakening and fatigue of masticatory muscles," although they did not report overt temporomandibular disorder problems. The authors postulate that these findings can be explained in terms of the pain-adaptation model, which states that motor activities are reduced in individuals experiencing pain. They also looked for associations between recent or current stress and the degree of sleep bruxism, based on psychological questionnaires, and found no specific relationships.

The authors conclude that this study confirms that the SB-RDC developed 10 years ago "facilitates a high level of discrimination between sleep bruxers and control subjects," and it also confirms the hypothesis that "pain is [more] frequently recorded among sleep bruxers who display low frequencies of jaw muscle contractions." For clinicians, this suggests the need to sort out bruxers and facial pain patients according to this model and to recognize that oral appliances made for true bruxers may be primarily for tooth protection, while those made for morning pain patients may be intended to reduce pain by altering nocturnal jaw behaviors. *(CSG)*

Baliki MN, Geha PY, Apkarian AV, Chialvo DR. Beyond feeling: Chronic pain hurts the brain, disrupting the default-mode network dynamics. J Neurosci 2008; 28: 1398–1403.

This interesting paper introduces a relatively new aspect of brain function that is affected by having chronic pain. It already is known that patients with chronic pain have depression, sleep disturbances, and decision-making abnormalities, suggesting that other non-pain brain areas are affected by having chronic pain. These authors build on previous investigations of the "default-mode network" (DMN), which exists in cortical regions known to be active at rest; this network is characterized by "balanced positive and negative correlations between activities in component brain regions." Previous imaging studies have shown that DMN balance can be disrupted in various clinical disorders such as autism, Alzheimer's disease, depression, schizophrenia, and attention-deficit hyperactivity disorder. However, nobody has previously studied the impact of chronic pain on this important homeostatic network. Therefore, these authors conducted a study of chronic back pain patients, using functional magnetic resonance imaging (fMRI) to study the DMN as these patients performed a simple visual attention task. This experimental protocol enabled them.0 to investigate whether some of the impairments in chronic pain patients might be due to disruption of that network.

The visual task involved the use of a finger-spanning device as the subject followed changes in the height of a bar on a computer screen while the fMRI images were acquired synchronously. Results were that the chronic pain patients performed as well as control subjects in doing this task, but there were significant differences in brain activity between the groups, as demonstrated by 3 different methods of analysis. This is the first study demonstrating that a group of chronic pain patients exhibit severe alterations involving functional connectivity in the DMN brain regions. The fact that chronic pain patients could perform the experimental task while experiencing a disruption in brain activity raises the question of how other behaviors are impaired by the altered brain activity. Because chronic pain patients report a constant (but fluctuating) perception of pain, their brains are never "at rest," so it is not surprising to find the altered resting state in these subjects. It has been proposed that the main function of the DMN is to provide a balance of opposing forces, so finding an unbalanced DMN in chronic pain patients suggests that these functions may be compromised. What is not known is whether long-term interference with normal DMN activity will eventually result in neuroplastic changes that are irreversible. The authors conclude by observing that: "Unraveling the mechanisms involved [in this phenomenon] would be critical to understand brain changes underlying cognitive and behavioral alterations commonly seen in chronic pain patients." *(CSG)*