Development of New Pain Management Strategies

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Abstract: The continued development of more effective and predictable methods for pain control is a process that combines the best efforts of basic and clinical scientists. This review explores the developing themes of clinical pain management strategies that are emerging from molecular, cellular, and physiologic research into pain mechanisms and emphasizes the unique opportunity that several years of well-controlled clinical trials affords the dental education community to provide evidence-based learning in pain treatment strategies.

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Researchers armed with the basic science knowledge of acute and chronic pain mechanisms are constantly striving to develop novel therapeutic approaches to the treatment of these disabling disorders. With regards to pharmacological strategies, the drug discovery process is a lengthy distillation, beginning with a preclinical phase in which compounds are tested first in vitro, and those few that give promising results are next analyzed in living systems or models. For agents that pass preclinical muster, the clinical phase of testing involves human trials that initially examine tolerability and then effectiveness in relatively small populations over short periods of time. If the drug in question continues to show encouraging results, trials with much larger patient populations over longer intervals are undertaken. If you imagine this process as a funnel into which prospective pharmacological agents are poured, the number of bona fide analgesics that exit are far fewer than the number that entered. Given the tortuous and expensive nature of drug development, the importance of a sound basic science foundation becomes clear.

What, then, are the developing themes of clinical pain management strategies that are emerging from basic research into pain mechanisms? Professor Sessle provides an elegant summary of the key developments in pain research, and his work complements other recent contributions to this literature.[1-3] We will divide an analysis of these findings into two broad categories: clinical implications of physiologic (systems) research and clinical implications of cellular and molecular research.

Clinical Implications of Physiologic (Systems) Research on Pain Mechanisms

A major finding from basic research on pain physiology is that pain perception is a dynamic state. Unlike other senses such as touch, the threshold and responsiveness of the pain system can be dramatically increased within just a few seconds of an appropriate stimulus. For example, injection of a small amount of capsaicin into the skin of volunteers produces a large area of heightened pain sensitivity over much of the arm.[4] This change in the pain system is measured in two dimensions. Allodynia is defined as a reduction in pain threshold to the point where non-noxious stimuli are now perceived as painful. Hyperalgesia is defined as an increase in the magnitude of pain perception, so that a previously painful stimulus is now perceived as having a larger magnitude of perceived pain. A good example is a sunburn: allodynia is represented by the pain perceived

when wearing a T-shirt (that is, reduced pain threshold) and hyperalgesia is represented by the increased pain perception when someone slaps your back (that is, increased pain responsiveness).

This dynamic change in the pain system also occurs in the orofacial region. For example, stimulation of pulpal nociceptors in one molar produces a mechanical allodynia to a large area of the rat's face.[5] Endodontists employ the concept of allodynia when performing clinical exams.[6] The percussion test of a suspected tooth represents a systematic evaluation for the presence of mechanical allodynia, and a positive test is interpreted as due to active inflammation in the periradicular region of the suspected tooth. Similarly, the palpation of orofacial muscles in evaluating a chronic pain patient represents a systematic evaluation of mechanical allodynia in muscles. Continued basic research into the mechanisms of mechanical allodynia may well lead to the development of novel therapeutic strategies for management of orofacial pain.

One of the key events that mediates this transition from a "normal" state to an enhanced pain state is a barrage of impulses along certain peripheral nerves. Basic research has shown that this transition generally requires repeated discharges from the unmyelinated (C fiber) class of nociceptors. These neurons represent the largest class of neurons innervating orofacial tissues such as dental pulp.[7] Stimulation of pulpal or TMJ C nociceptors in the rat produces this change in the pain state within just a few minutes of neuronal discharge.[8] This effect has led to the suggestion that clinicians might be able to provide "preemptive" drug therapy to block these discharges and thereby reduce the development of postoperative allodynia or hyperalgesia. The logical drug class to test this hypothesis is the local anesthetics. Clinical trials in oral surgery patients have shown that a single preoperative injection of bupivacaine, a long-acting local anesthetic, results in lower pain reports in patients undergoing general anesthesia for the removal of impacted third molars, even forty-eight hours after extraction.[9] (See Figure 1.) Additional studies have replicated this finding by demonstrating that infiltration injection of bupivacaine into the surgical site (tonsillectomy) results in a reduced level of postoperative pain as compared to a placebo injection.[10] (See Figure 2.) Thus, postoperative pain control may well begin with the administration of an effective and deep level of local anesthesia.

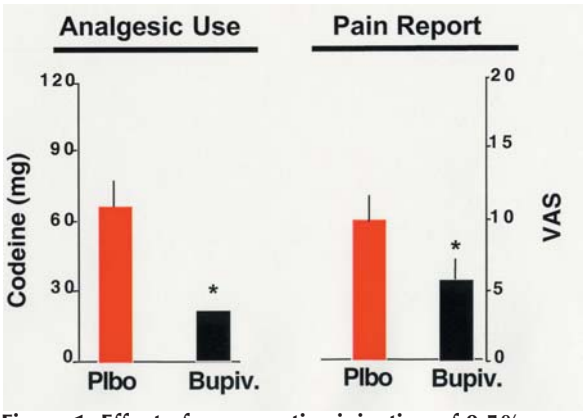

Figure 1. Effect of preoperative injection of 0.5% bupivacaine with 1:200,000 epinephrine or placebo (saline with 1:200,000 epinephrine) on postoperative pain and analgesic consumption. Patients underwent general anesthesia, then received test drug by inferior alveolar nerve block injection, then surgical removal of impacted third molars. The analgesic use and pain report were collected at 48h after the surgical procedure. *p<0.05 vs placebo. Figure redrawn from: Gordon SM, Dionne RA, Brahim J, Jabir F, Dubner R. Blockade of peripheral neuronal barrage reduces postoperative pain. Pain 1997;7:209-15.

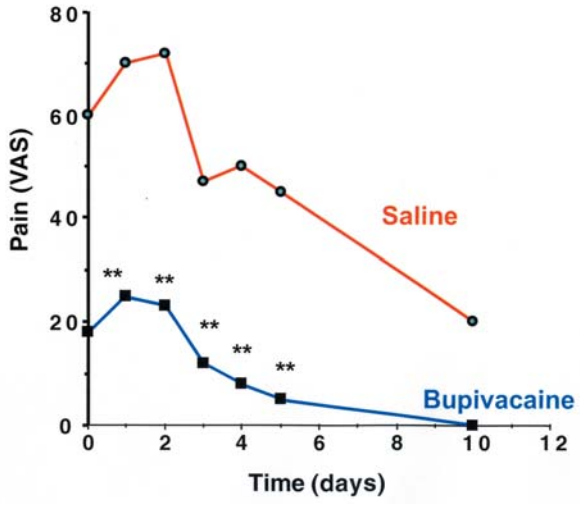

Figure 2. Effect of preoperative injection of 0.5% bupivacaine with 1:200,000 epinephrine or placebo (saline with 1:200,000 epinephrine) on postoperative pain. Patients underwent general anesthesia, then received test drug by infiltration injection, then underwent tonsillectomy. The pain reports were collected at various times after the surgical procedure. **p<0.01 vs placebo. Figure redrawn from: Jebeles JA, Reilly JS, Gutierrez JF, Bradley EL Jr, Kissin I. Tonsillectomy and adenoidectomy pain reduction by local bupivacaine infiltration in children. J Ped Otorhinolaryngol 1993;25:149-54.

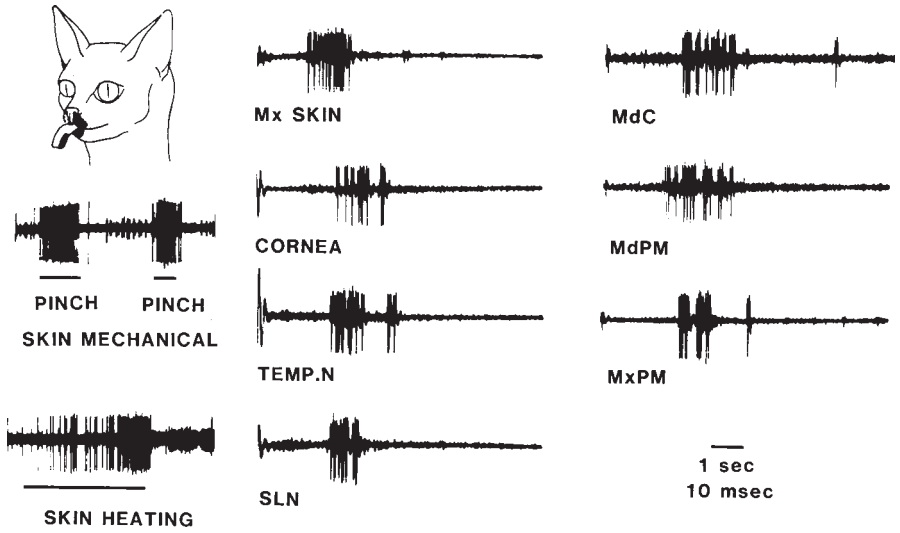

Figure 3. Recording of a nociceptive neuron in the trigeminal nucleus caudalis of an anesthetized cat. The arrowhead illustrates the receptive field (RF) for the neuron. For each orofacial tissue listed, the associated recording shows the responsiveness of the caudalis neuron after stimulation of the respective tissue. The data indicate that multiple sensory neurons converge onto the same central trigeminal neuron. These data support the convergence theory of referred pain. Used with permission from: Sessle B, Hu J, Amano N. Convergence of cutaneous, to pulp, visceral, neck and muscle afferents onto nociceptive and non-nociceptive neurons in trigeminal subnucleus caudalis (medullary dorsal horn) and its implications for referred pain. Pain 1986;27:219-35.

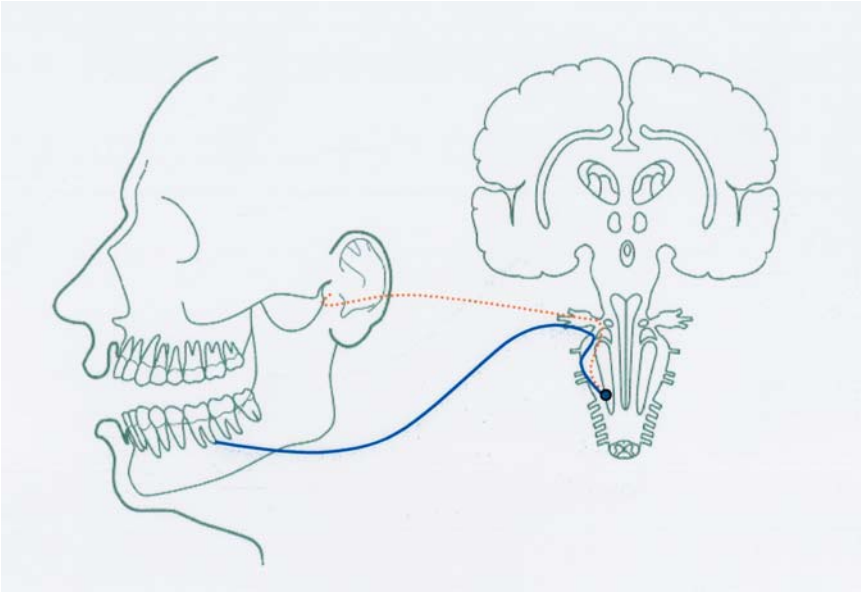

Figure 4. Schematic illustration of the convergence theory in a patient. Neurons innervating the first molar pulp and preauricular tissues converge onto the same central trigeminal neuron in the nucleus caudalis. In this example, pain may be perceived in the preauricular area, but is due to activation of pulpal nociceptors due to irreversible pulpitis. An inferior alveolar nerve block can be considered as a diagnostic test since it would be expected to reduce the preauricular pain under these conditions. Used with permission from: Hargreaves KM, Seltzer S: In: Seltzer S, Bender IB. Dental pulp. Carol Streams, IL: Quintessence Books, 2002.

Other physiologic studies conducted in animals have led to a greater understanding of referred pain. Referred pain represents an important clinical problem in the management of both acute and chronic orofacial pain.[11] These animal studies have led to the realization that peripheral sensory neurons can converge onto the same central projection neuron. In the experiment shown in Figure 3, the same central neuron (in the N. caudalis) received sensory input from a number of different orofacial regions including maxillary and mandibular teeth.[12] This and other studies have led to the convergence theory of referred pain. This theory is thought to explain the well-recognized phenomenon that patients with cardiac pain (for example, MI) report pain down the left arm. In the orofacial region, patients may perceive pain localized to the ear

even though it is originating from pulpal nociceptors (Figure 4). This is why the use of local anesthetics play an important diagnostic function. In the example shown in Figure 4, blockade of the inferior alveolar nerve will reduce the earache by virtue of blocking the pulpal nociceptors that are activated in response to pulpitis.

Clinical Implications of Cellular and Molecular Research on Pain Mechanisms

Numerous studies have expanded our understanding of pain by focusing on the key role that receptors, signal transduction pathways, and genes play in mediating the response to inflammation or nerve injury.[2,3,5] Greater understanding of these processes may lead to biochemically based diagnostic tests for pain conditions,[13] as well as identification of new targets for analgesic drug development. Although this approach is the focus of a considerable amount of ongoing research, some clinical progress has been made.

The development of the selective cyclooxygenase 2 (COX-2) inhibitors represents the first clinical introduction of an analgesic drug designed to selectively modulate the activity of a newly expressed protein. For example, tissue levels of the COX-2 enzyme are quite low in normal dental pulp, but are substantially increased in teeth with a clinical diagnosis of irreversible pulpitis.[14] In addition, at least one COX-2 inhibitor, rofecoxib, is analgesic in acute dental pain due to extraction of third molars (Figure 5). However, its time for onset of analgesia and the total analgesic response is quite similar to ibuprofen 400 mg, suggesting that this drug class may not have greater analgesic efficacy in acute dental pain than traditional non-steroidal antiinflammatory drugs.[15] Several other examples of drugs based on identified cellular or molecular targets are in earlier stages of development.

As described above and in Sessle's article (in this issue), the development of hyperalgesia and allodynia are thought to be due in part to an intense afferent barrage of nociceptors. Several studies have implicated the release of glutamate, an excitatory neurotransmitter, in mediating this effect via activation of its receptors. There are three broad classes of glutamate receptors in the ligand-gated ion channel family: NMDA, kainite, and AMPA receptors. Investigators have proposed that antagonists to these receptors may block the development of hyperalgesia or allodynia in patients. Some of these drugs have been developed and tested in clinical trials. The an-

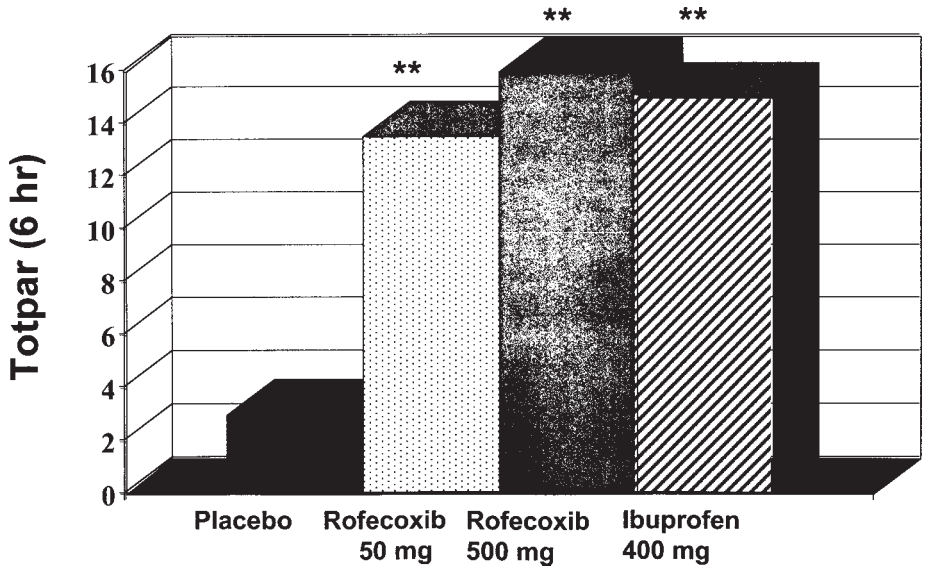

Figure 5. Comparison of placebo to rofecoxib 50 and 500 mg to ibuprofen 400 mg for relief of post-surgical pain. Redrawn from: Ehrich E, Dallob A, DeLepeleire I, Van Hecken A, Riendeau D, Yuan W, et al. An immunohistological study on cyclooxygenase-2 in human dental pulp. Clin Pharm Therap 1999;65:336-47.

algesics effects of a kainate/AMPA antagonist on postoperative pain following extraction of third molars is presented in Figure 6.[16] Interestingly, the antagonist LY293558 blocked evoked pain, but not spontaneous postdental pain. The evoked pain was a test for mechanical allodynia: patients were asked to rate their pain after opening their mouths wide at various times after extraction of the impacted third molars. Thus, the kainate/AMPA antagonists appear to have more efficacy for reducing mechanical allodynia than spontaneous pain. This sheds important light on pain mechanisms, although the clinical utility of this drug class for acute orofacial pain may be limited.

Another approach for developing analgesics is based on cellular identification of nociceptors. It is well recognized that the nociceptors constitute the predominant class of neurons that innervate dental pulp. Accordingly, one can place a fluorescent dye in dental pulp and, after a period of time, the dye will diffuse in a retrograde fashion to the cell bodies in the trigeminal ganglion. When viewed under the microscope, the pulpal neurons literally glow under the appropriate conditions. Since these neurons are primarily nociceptors, investigators can evaluate which receptors are expressed on these neurons. This process provides a direct, biochemically based method for evaluating novel analgesics. Using this technique, McClesky's laboratory has demonstrated that pulpal neurons express the mu opioid receptor,and that opioids suppress the activity of these pulpal neurons in cell culture.[17] Thus, opioids, which have traditionally been thought to act only in the CNS, may possess peripheral analgesic activity in treating orofacial pain.[18]

The hypothesis of peripheral opioid analgesia has been tested in several clinical trials on dental pain patients.[19,20,21] In one study, the peripheral (intraligamentary) injection of morphine was compared to a local anesthetic and a placebo in patients suffering from odontalgia (primarily irreversible pulpitis).[19] As shown in Figure 7, the intraligamentary injection of morphine produced a significant dose-related analgesia in these endodontic pain patients. Control studies verified that this effect was peripherally mediated.[19] Peripherally selective opioids may provide a novel approach for managing inflammatory pain. According to this proposal, one could envision a formulation in which a combination of a local anesthetic and a locally active opioid could be used for management of severe pain in dental patients.

One of the most interesting research findings of the last twenty years is the realization that the nervous system changes in response to injury. For example, peripheral neurons actually grow into inflamed tissue, with extensive arborization into the area of injury. This was first shown in the elegant studies of Byers and colleagues,[22] but more recently several studies have demonstrated that human dental pulps display the same type of neuronal growth in regions affected by carious lesions.[23] This change in nociceptors has several important implications since it may predispose patients to pain perception (due to increased density of nociceptive neurons in areas of inflammation) and may be important in regulation of inflammation, pulpal necrosis, or wound healing.[1,24-26] The clinical implications are in two broad areas. First, do similar sprouting events occur in acute and chronic pain patients? If so, what molecular signals are required to reset these neurons back to their normal state? Second, can new drugs be developed to modulate the peripheral neuropeptide system to obtain better wound healing or control of infection?

Future Directions

Continued basic research into pain mechanisms is likely to achieve several important and clinically useful approaches to pain control. A dominant emerging theme is the view that dramatic progress in basic research will lead to the rational development of pain control strategies. According to this approach, continued basic research will reveal new hypotheses on pain mechanisms in experimental models. Insight into pain mechanisms will identify new targets for drug development. The lead agents in the drug development process must then be evaluated for efficacy in clinical phase II trials. This is a critical proof of concept step since some drugs (such as the substance P [NK1] antagonists) are more active in animal models than in clinical trials.[27] Agents of sufficient efficacy and safety will then be reviewed by the FDA for approval prior to their introduction into the marketplace. However, clinicians should not simply adopt any drug introduced as a new analgesic. Instead, this is the point at which evidence-based systematic reviews are required to develop clinical recommendations on relative drug efficacy and side-effect liability.

Evidence-Based Treatment and Educational Strategies

The development of evidenced-based treatment strategies is a major initiative in all of health care, including dentistry.[28,29] Although a detailed examination of each individual clinical technique often leads to the impression that there is insufficient evidence available for a systematic review, this is not the case for pain control. The legacy of three decades of well-controlled clinical trials in pain offers the opportunity for quantitative systematic reviews of pain control methods.[30]

These systematic review studies often use meta-analyses to determine the number needed to treat (NNT). The NNT is the number of patients needed to be treated on the active drug to obtain one additional patient with pain relief as compared to the placebo treatment. Thus, the NNT is a measure of the relative superiority of an analgesic over the placebo and permits pooling data from multiple clinical trials that satisfy certain a priori criteria.[31] A lower NNT for an analgesic is better than a higher NNT: an NNT of three means that only three patients needed to be treated on the active drug in order to have one more patient with pain relief as compared to the placebo. In contrast, an NNT of ten means that ten patients

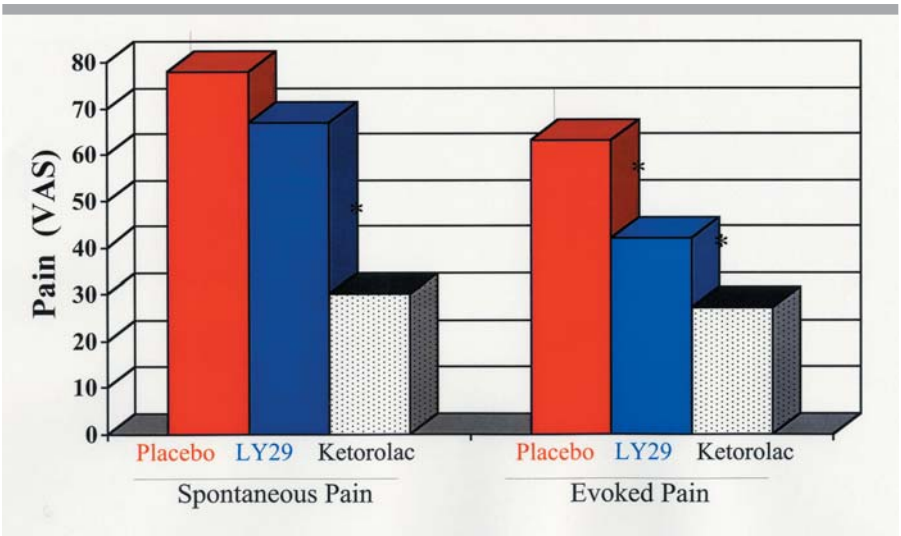

Figure 6. Effect of placebo treatment, or LY293558 (1.2 mg/kg iv), a kainite/AMPA receptor antagonist, or ketorolac (30 mg iv) on postoperative pain levels after extraction of impacted third molar teeth. Patients underwent surgical extraction of third molars under local anesthesia and were administered a study medication when they experienced moderate to severe postoperative pain. Drug effects were measured for spontaneous pain (LEFT panel) and for pain evoked by opening the mouth widely (RIGHT panel). *p<0.05 vs placebo. Figure redrawn from: Gilron I, Max M, Lee G, Booher S, Sang C, Chappell A, Dionne R. Effects of the 2-amino-3-hydroxy-5-methyl-4-isoxazole-proprionic acid/kainate antagonist LY293558 on spontaneous and evoked postoperative pain. Clin Pharm Therap 2000;68:320-7.

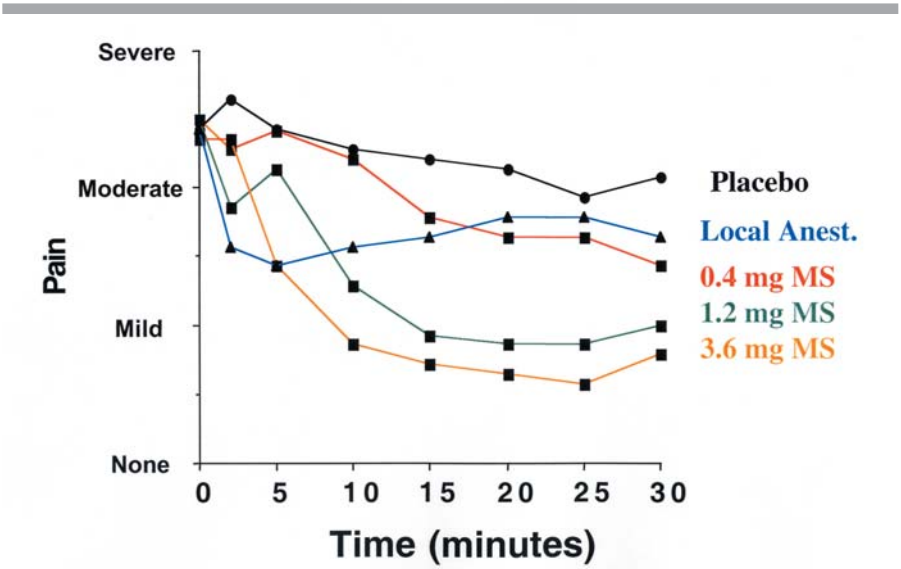

Figure 7. Effect of intraligamentary injection of placebo, local anesthetic (2% mepivacaine with 1:20,000 levonordefrin) or morphine sulphate (0.2, 1.2, or 3 mg) on endodontic pain. Patients who presented to the clinic and provided informed consent were administered test medication and followed for 30 min. Data redrawn from: Dionne RA, Lepinski AM, Gordon SM, Jaber L, Brahim JS, Hargreaves KM. Analgesic effects of peripherally administered opioids in clinical models of acute and chronic inflammation. Clin Pharmacol Therap 2001;70(1):66-73.

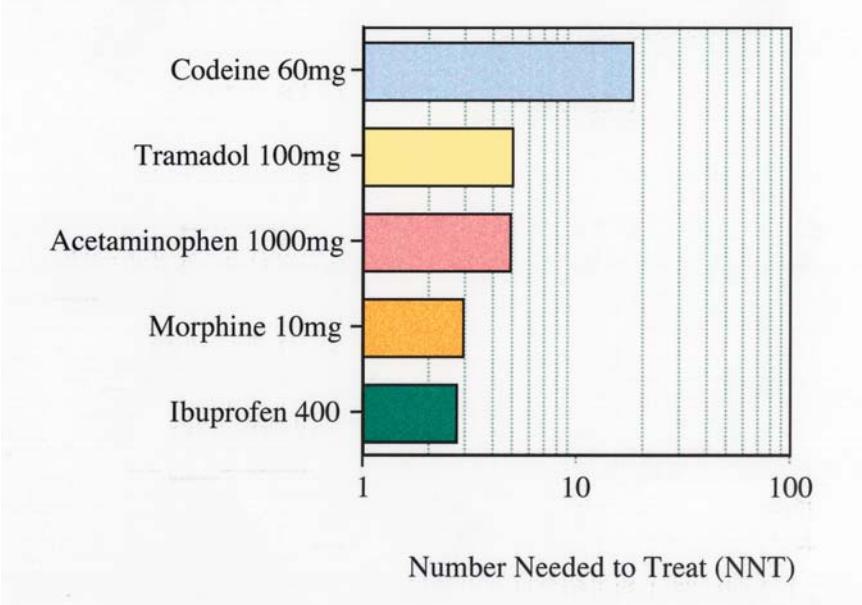

Figure 8. A comparison of the relative analgesic activity of various drugs for acute pain. The data have been analyzed as the number needed to treat (NNT). The NNT is a measure of relative superiority of an analgesic over placebo treatment; the lower the NNT, the greater the relative analgesic activity (see text for additional details). Figure redrawn from: McQuay H, Moore R. An evidence-based resource for pain relief. Oxford: Oxford University Press, 1998:187-92.

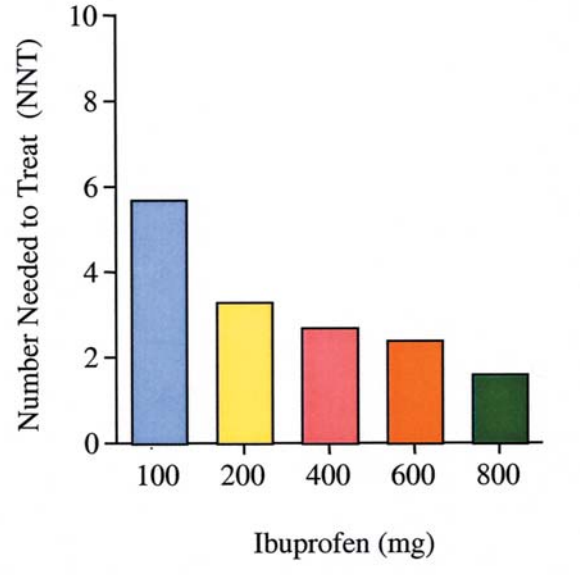

Figure 9. Ibuprofen dose-response relationship for acute pain. The data have been analyzed as the number needed to treat (NNT). The NNT is a measure of relative superiority of an analgesic over placebo treatment; the lower the NNT, the greater the relative analgesic activity (see text for additional details). Figure redrawn from: McQuay H, Moore R. An evidence-based resource for pain relief. Oxford: Oxford University Press, 1998:78-93.

must be treated with the active drug to have one more patient with pain relief as compared to the placebo. As shown in Figure 8, ibuprofen 400 mg has an NNT of about 2.6, whereas codeine 60 mg has an NNT of about 18.[30] Thus, ibuprofen 400 mg provides considerably more analgesia than codeine 60 mg.

Additional systematic reviews have evaluated dose-response relations and nonpharmacological treatment. Figure 9 illustrates the ibuprofen dose-response curve and indicates that an increasing magnitude of analgesic activity is observed over a 100-800 mg dose range.[32] Table 1 summarizes a systematic review on the effectiveness of transcutaneous electrical stimulation (TENS), a nonpharmacological pain treatment.[33] The available evidence indicates that TENS is reported as effective in poorly controlled studies, but is much less effective in well-controlled studies. Taken together, these findings illustrate the established application of systematic reviews in developing evidence-based recommendations for pain management. Evidence-based care can be introduced into our curricula today—and perhaps the best starting point is on pain control.

Table 1. Summary of clinical studies on analgesic activity of TENS

Type of Clinical Trial	Did TENS Produce Analgesia?	
	Yes	No
Randomized Clinical Study	2	15
Inadequate Clinical Study	17	2

Data from McQuay[33]

Conclusions

The continued development of more effective and predictable methods for pain control is a process that combines the best efforts of basic and clinical scientists. In many ways, this process represents a unique teaching opportunity, permitting the integration of the basic sciences and the clinical sciences, together with a focus on lifelong learning as epitomized by the evidence-based approach to therapeutics. This thematic combination is likely to not only serve as a useful pilot program for dental education, but may well lead to improved patient care.

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