Pain: From Theory to Practice and Beyond
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Course Description
The Plenary session on Pain covers a broad range of basic science and practical clinical knowledge- the topics include standard and emerging pharmacologic treatments of neuropathic pain, alternative/non-drug treatments and their efficacy, evaluation of epidural steroids and other interventions in low back pain, basic science of sodium channels and neuropathic pain, what we have learned from cutting edge neuroimaging, and finally a lecture on the epidemic of opioid related deaths and how to manage and withdraw those taking large (>150mg morphine equivalents) doses.

Intended Audience
This course is intended for Neurologists, Physiatrists, and others who practice neuromuscular, musculoskeletal, and electrodiagnostic medicine with the intent to improve the quality of medical care to patients with muscle and nerve disorders.

Learning Objectives
Upon conclusion of this program, participants should be able to:
(1) describe the role of the brain in the perception and modulation of pain.
(2) identify the factors that modify perception of pain and how the brain contributes to individual differences in pain.
(3) recognize how functional neuroimaging contributes to the knowledge of pain.
(4) evaluate evidence-based support for currently available spine interventional strategies for pain management.
(5) incorporate both pharmacologic and nonpharmacologic strategies for pain management.
(6) apply principles of multimodal management to neuropathic pain.
(7) utilize knowledge of controlled substance statutes to optimize pain management in clinical practice.

Activity Profile
This enduring material activity is a reproduction of the printed materials from a course at the AANEM Annual Meeting (October 6-9, 2010). Physician participation in this activity consists of reading the manuscript(s) in the book and completing the clinical and CME questions.

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Expiration Date: January 10, 2014. Your request to receive AMA PRA Category 1 Credits™ must be submitted on or before the credit expiration date.
Duration/Completion Time: 3 hours

Accreditation and Designation Statements
The American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.
The AANEM designates this enduring material for a maximum of 3.0 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.
Pain: From Theory to Practice and Beyond

Faculty

Vera Bril, MD, FRCPC
Director of Neurology
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Dr. Bril is a professor of medicine (neurology) at the University of Toronto, director of neurology at University Health Network and Mount Sinai Hospital and the Krembil Family Chair in Neurology. She has particular expertise in the diagnosis and management of patients with complex neuromuscular disorders. Her research interests have centered on the diagnosis and evidence-based treatment of myasthenia gravis, inflammatory polyneuropathies, and diabetic sensorimotor polyneuropathy. Her work has helped set the standards for electrophysiological investigations in the definition and evaluation of the progression of chronic polyneuropathies. Her research has helped establish the role of intravenous immunoglobulin in the treatment of myasthenia gravis and the Guillain-Barré syndrome, and the long-term treatment of chronic inflammatory demyelinating polyneuropathy. She has acted in an advisory capacity to Health Canada and the Federal Drug Administration. Dr. Bril also serves as the deputy physician-in-chief for economic affairs for the Department of Medicine at the University Health Network and Mount Sinai Hospital and chair of the economics committee. She is part of the Department of Medicine Executive Committee and helps administer this group of 300 physicians. Dr. Bril is certified in electrodiagnostic medicine by the American Board of Electrodiagnostic Medicine.

Anthony E. Chiodo, MD
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After completing his medical school training in his home state at the University of Connecticut Health Center, Dr. Chiodo started his psychiatric career at the University of Michigan Hospital where he completed his residency and neuromuscular fellowship. He had a private practice in pediatric rehabilitation at Methodist Hospital in Indianapolis and was the medical director of physical medicine and rehabilitation in Farmington, New Mexico, on the border of the Navajo reservation. Dr. Chiodo returned to the University of Michigan in 1998. His academic areas of interest include anatomic localization in electromyography, lumbosacral plexopathy after pelvic trauma, and clinical electrodiagnostics. He is board certified in pain medicine, spinal cord injury, and electrodiagnostic medicine, applying his research emphasis in electrodiagnostics to those areas of specialty as well. He has continued his work in the care for the disabled in underserved areas that he started in New Mexico by working on sustainable medical rehabilitation program development in Ghana in West Africa.

Gary M. Franklin, MD, MPH
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Medical Director
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Dr. Franklin obtained his medical degree from George Washington University, and the his masters in public health from the University of California at Berkeley. He is a board-certified neurologist whose current positions are 1) research professor, Departments of Environmental and Occupational Health Sciences, and Medicine (Neurology), University of Washington School of Public Health, and 2) medical director, Washington State Department of Labor and Industries. Dr. Franklin is the chair of the Washington State Agency Medical Directors Group, and has led efforts by the state agencies in Washington in the development of evidence-based health policy. His current research interests include population-based outcome studies for work-related musculoskeletal disorders, health care delivery research, and research to predict disability and generate models of disability prevention in workers’ compensation.

Course Chair: Laurence J. Kinsella, MD

The ideas and opinions expressed in this publication are solely those of the specific authors and do not necessarily represent those of the AANEM.
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Dr. Levine is a graduate of Duke Medical School. His neurology residency and fellowship in neuromuscular diseases was completed at Washington University in St Louis. He joined Phoenix Neurological Associates in 1999. Since that time he has created and directed the peripheral neuropathy center at Good Samaritan Hospital as well as the amyotrophic lateral sclerosis (ALS) clinic at Good Samaritan Hospital. He is also the director of the neurophysiology department at Good Samaritan Hospital. He is the past-president of the Arizona Neurology Association. Dr. Levine conducts phase II-IV clinical research in many fields of neuromuscular diseases including neuropathy, myositis, and ALS. He continues to publish in peer reviewed journals and to teach courses at the American Academy of Neurology and the American Association Neuromuscular & Electrodiagnostic Medicine. Dr. Levine is certified in electrodiagnostic medicine by the American Board of Electrodiagnostic Medicine.

S. Rock Levinson, PhD  
Professor  
Department of Physiology and Biophysics  
University of Colorado School of Medicine  
Aurora, Colorado  

S. Rock Levinson received his PhD for thesis work conducted in the Physiological Laboratory at the University of Cambridge. He then did postdoctoral work in the Department of Chemistry at the California Institute of Technology. He subsequently assumed a position at the University of Colorado School of Medicine, where he is currently professor of physiology and biophysics. Dr. Levinson’s current research interests are in the role of ion channels in pain and in the regulation of ion channel expression in neurodegenerative disorders. Dr. Levinson is also a founder of Biotricity Medical, Inc., a startup company developing a novel living bioelectricity generator for powering implanted biomedical devices, such as deep brain stimulators and sensory prostheses.

Sean Mackey, MD, PhD  
Associate Professor of Anesthesia  
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Stanford University  
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Dr. Mackey is an associate professor of anesthesia (and of neurology and neurological sciences, by courtesy) at Stanford University. Dr. Mackey completed his undergraduate and Masters’ degree studies in bioengineering at the University of Pennsylvania and received a PhD in electrical engineering and his medical degree at the University of Arizona. He went on to Stanford where he completed his anesthesiology residency and a fellowship in pain management and subsequently joined the faculty. While there, he founded and directed the Regional Anesthesia program. He is currently the chief of the Stanford Pain Management Division. As director of the Stanford Systems Neuroscience and Pain Laboratory, Dr. Mackey’s primary research interest involves the use of advanced research techniques such as functional and structural neuroimaging, psychophysics, and neurobehavioral assessment to investigate the neural processing of pain and neuronal plasticity in patients with chronic pain. Dr. Mackey has served as principal investigator and investigator for multiple National Institutes of Health (NIH), foundation, and industry-sponsored grants to investigate chronic pain and to investigate novel analgesics for acute and chronic pain. He is a member of several professional organizations, is on the Board of Directors for the American Academy of Pain Medicine, is a member of the NIH National Institute on Drug Abuse (NIDA) study section, and serves on the editorial board and is a reviewer for multiple scientific journals. Dr. Mackey has published over 60 articles and book chapters. He annually presents papers and lectures at both national and international pain management and anesthesiology meetings.

Dr. Bril is a consultant and speaker for Talecris. She also received research support from Esai Pharmaceuticals and Johnson & Johnson. Any conflict of interest was resolved according to ACCME Standards.

Dr. Levine was a scientific consultant for Allergan. Any conflict of interest was resolved according to ACCME Standards.

Dr. Levine is on the Speakers Bureau for Eli Lilly, Pfizer, and Talecris. Any conflict of interest was resolved according to ACCME Standards.

All other authors/faculty have nothing to disclose.
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GENERAL CONSIDERATIONS

Neuropathic pain (NP) is a prevalent problem presenting a challenge in management to all physicians and to neuromuscular physicians and rehabilitation physicians in particular. The successful management of patients with NP combines the science and art of medicine without a cookbook approach that would provide a single recipe for all patients. In fact, patients with NP are often refractory to commonly used interventions or suffer such adverse reactions that the treatment must be withdrawn. Other elements that contribute to NP, such as comorbid depression, are often not addressed and yet will affect the outcome of treatment. Finally, as treatment of NP can be difficult, physicians are urged to avoid the ostrich approach of ignoring this debilitating problem in the hope that it will disappear. Quality of life (QOL) studies have shown that patients with NP suffer chronically and significantly, and it is the physician’s role to try to alleviate this distress and improve the patient’s ability to function and their overall QOL.

Some authorities suggest that the choice of pharmacological agent to treat NP should be guided by the character of the pain, as the response may be improved by matching medication to pain character. Many patients have multiple types of pain and it is rare to be able to categorize patients this clearly. Further, NP studies generally have not separated patients into categories and so the evidence for efficacy in patients with NP does not rely on such categorization. Further work needs to be done in this area to be able to apply this approach in the clinic.

Treatment of NP can be divided into pharmacological and nonpharmacological modalities. Nonpharmacological modalities will not be addressed further. The pharmacological treatments are subdivided into topical, oral, and intravenous preparations, as outlined in Figure 1. The oral medications are generally grouped as analgesic agents or adjuvant analgesic agents, meaning that the drug is not a primary analgesic but has analgesic properties. Opioids are discussed in detail elsewhere and will be mentioned here only briefly. Adjuvant analgesic agents include anticonvulsants, antidepressants, and others. Monotherapy is in widespread use, but combination therapy has been advocated more recently. The evidence base for the NP treatment contains many studies on painful diabetic polyneuropathy and postherpetic neuralgia (PHN). Other smaller studies are available for traumatic nerve injury and other NP disorders such as human immunodeficiency virus (HIV)-related neuropathy, central pain, and trigeminal neuralgia. This evidence will not be reviewed in detail here. An evidence-based practice parameter on the treatment of painful

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**Figure 1** Outline of Pharmacological Treatment of Neuropathic Pain

ACD=anticonvulsant drugs, ADD=antidepressant drugs

Pharmacologic Treatment of Neuropathic Pain

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diabetic neuropathy (PDN) is being written by the American Association of Neuromuscular & Electrodiagnostic Medicine, the American Academy of Neurology, and the American Academy of Physical Medicine and Rehabilitation and is anticipated to be published in the coming year. In general, the response to treatment with any particular agent in different neuropathies may be similar to the treatment results in PDN, although the evidence base often is more limited. There are exceptions to this rule, such as studies on HIV-related painful neuropathy showing absence of the analgesic response observed in PDN.8

One limitation in many older studies is that efficacy is measured by pain reduction only is and not always on the same pain scale. Many studies report use of an 11-point Likert scale to measure pain at baseline and after treatment. The degree of pain relief often is not large, although the difference from baseline compared to placebo is significant. Fewer studies measure QOL, or other important elements such as patient activity/functional level, depression, or sleep disturbance. The reports that do include these elements tend to be recently published studies of novel drugs. Furthermore, most studies are generally shortterm treatment trials with a virtual lack of longterm, placebo-controlled studies.

**TOPICAL TREATMENT**

The topical agents used for NP treatment are the local anaesthetics, opioids, capsaicin, and nitrate spray.9-15 Lidocaine, fentanyl, capsaicin, and glyceryl trinitrate can be administered as patches.9,12,14,15 These treatments have the advantage of not having systemic effects due to low or nondetectable systemic drug levels. Lidocaine patches can cause localized skin reactions with erythema and localized rash, but patients with diverse painful neuropathies experience pain relief.15 Lidocaine as a topical gel is most helpful for patients with focal NP, such as PHN, but not for central pain.7

Topical capsaicin, although effective in clinical trials in relieving pain, has limited clinical usefulness due to the adverse effect of burning pain related to the presence of capsicum (hot chiles) in capsaicin. In effect, exposure to hot water or hot weather with diaphoresis can induce burning discomfort that limits usefulness of this treatment. Other patients are unable to apply the cream four times daily. In other cases, the burning is too widespread for the patient to apply the treatment comfortably. The advantage is that capsaicin does not have systemic side effects and so can prove useful in patients with comorbidities on multiple drugs who have limited tolerability to most oral agents. Capsaicin is now available as an 8% patch and studies have shown that a single 1-hour 8% patchapplication can provide 3 months of relief from pain associated with PHN.14

**ORAL TREATMENT**

**Opioids**

The use of opioids in nonmalignant chronic pain has been limited in the past. Initially, the view was that opioids lacked efficacy in relieving NP. However, many studies have shown that different opioids such as morphine, methadone, oxycodone, levorphanol, and tramadol are effective in reducing NP.7,16,20 Although tramadol is thought to be only weakly opioid in nature, the side effect profile resembles that of opioids in general (somnolence, constipation, dizziness, nausea, cognitive impairment, and ataxia). Tramadol also inhibits the reuptake of norepinephrine and serotonin and combination treatment with other serotonergic medications is hazardous.

Combination therapy (gabapentin with morphine, tramadol with acetaminophen) may be advantageous with more pain relief at lower doses than observed with monotherapy.21,22 The issues with opioids are dependency, addiction with abuse, and overdose.7 Opioids generally are not considered first-line therapy for chronic, nonmalignant NP.7,8

**Antidepressants**

The tricyclic antidepressants (TCA) (amitriptyline, nortriptyline, and desipramine)23-27 and the selective serotonin and norepinephrine reuptake inhibitors (SSNRI) (duloxetine and venlafaxine) are effective in relieving NP.27 The TCA are effective mainly for PDN and PHN, but not for HIV neuropathy, spinal cord injury, neuropathic cancer pain, or chronic radiculopathy.7 These drugs are effective in patients with and without depression. The side effects are sedation, anticholinergic effects (dry mouth, constipation, and urinary retention), and orthostatic hypotension. Secondary amines (nortriptyline and desipramine) have the same analgesic effect as tertiary amines (amitriptyline and imipramine) but with better tolerability.28 The risk of myocardial infarction is likely not increased with TCA at doses less than 100 mg/day.29 Despite unclear evidence for risk of cardiac events with TCA, administration to elderly, at-risk patients should be done cautiously. Doses of TCA start low and are gradually titrated upward. Classically, the starting dose has been 10 mg/day titrated upward slowly. Most patients do not reach levels of greater than 75 mg/day due to lack of tolerability. The analgesic effect may take weeks to be observed and titration is performed at 2 week intervals. TCA are older medications and relatively inexpensive.

SSNRI are also effective for NP. Duloxetine is efficacious in PDN, but there is limited safety data as it is a recently developed drug. Nausea is frequent. Other side effects are dry mouth, constipation, anorexia, fatigue, drowsiness, dizziness, blurry vision, skin rash, pruritus, and mood changes. Doses of 30-60 mg/day are effective within 1 week. Venlafaxine is also effective in PDN and other painful polyneuropathies, but the effect is less certain in central NP, PHN, and postsurgical nerve pain. Doses are 150-225 mg/day with gradual titration over 2-4 weeks. In one study, electrocardiogram changes were observed in 5% of patients on venlafaxine.30 An outline of potential side effects of SSNRI treatment is shown in Table 1. Withdrawal of venlafaxine therapy should be gradual to avoid discontinuation syndrome.31 The SSNRI are newer agents and more expensive than TCA.
Anticonvulsants

Calcium Channel $\alpha_2-\delta$ Ligands

Gabapentin and pregabalin bind to the $\alpha_2-\delta$ subunit of the voltage-gated calcium channel and thereby decrease the release of glutamate, norepinephrine, and substance P. $^7$ $^3^2$ Gabapentin has been positive in peripheral and central NP disorders and also has improved sleep and QOL. The main side effects are drowsiness, dizziness, peripheral edema, and weight gain. Cognitive changes and gait impairment can also be observed. Doses are titrated to 3600 mg/day. Pregabalin has similar efficacy in peripheral and central NP and has side effects similar to gabapentin. $^3^2$ The starting dose is 75 mg once or twice daily and is titrated to 600 mg/day. The dose needs to be reduced in renal impairment. Pregabalin also has anxiolytic effects that may be beneficial in some patients. Both gabapentin and pregabalin are effective within 2 weeks and both are more costly than TCA as they are newer agents.

Other Anticonvulsants

Valproic acid is gamma-aminobutyric acid (GABA)-ergic and also inhibits glutamate/N-methyl-D-aspartate (NMDA) and has proven effective in reducing pain in PDN. $^7$ The effect is improved if combined with glyceryl trinitrate spray. $^{3^3}$ However, not all types of NP respond to valproic acid. $^{3^4}$ A major consideration is that valproic acid is teratogenic and its use should be avoided in women of child-bearing age. Other side effects are fatigue, dizziness, nausea, vomiting, tremor, hair loss, ataxia, weight gain, behavioral changes (depression), and skin rash. The initial dose is 500 mg two times a day titrated to 1500 mg three times a day slowly.

Tegretol is effective in trigeminal neuralgia and remains the agent of choice for this disorder although newer analogues may have fewer side effects. $^{3^5}$

Other novel anticonvulsants, such as the sodium channel blocker lamotrigine, are not clearly efficacious in PDN and other NP states. Similar inconclusive or negative results have been found for zonisamide (blocks voltage-gated sodium and T-type calcium channels), topiramate (sodium channel blocker), oxcarbazepine (sodium

<table>
<thead>
<tr>
<th>Side-effect</th>
<th>Patients</th>
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<tbody>
<tr>
<td>Nausea</td>
<td>37%</td>
</tr>
<tr>
<td>Headache</td>
<td>25%</td>
</tr>
<tr>
<td>Sleepiness</td>
<td>23%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>22%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>19%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>18%</td>
</tr>
<tr>
<td>Constipation</td>
<td>15%</td>
</tr>
<tr>
<td>Nervousness</td>
<td>13%</td>
</tr>
<tr>
<td>Raised blood pressure</td>
<td>13%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>12%</td>
</tr>
<tr>
<td>Sweating</td>
<td>12%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>11%</td>
</tr>
<tr>
<td>Male sexual dysfunction</td>
<td>12%</td>
</tr>
<tr>
<td>Female sexual dysfunction</td>
<td>2%</td>
</tr>
</tbody>
</table>

Table 1 Side-Effects of a selective serotonin and norepinephrine reuptake inhibitor

Figure 2: The Number Needed to Treat for Pharmacological Treatments $^{3^8}$

\[ n_{active}/n_{placebo} \]

\[ 266/277 \]

\[ 81/81 \]

\[ 119/116 \]

\[ 13/13 \]

\[ 97/97 \]

\[ 14/11 \]

\[ 183/204 \]

\[ \text{n = number; NNT = number needed to treat; NMDA = N-methyl-D-aspartate; SSRI = selective and more pinephrine reuptake inhibitor; TCA = tricyclic antidepressants} \]
channel blocker), and lacosamide (enhances slow inactivation of voltage-gated sodium channels).8

**INTRAVENOUS THERAPY**

Intravenous treatment is not in widespread use for chronic NP. However, in selected circumstances, in patients with severe, acute pain (for example, as in diabetic neuropathic cachexia), or with chronic and debilitating pain, intravenous therapy may be tried when other approaches fail to provide relief. Both intravenous antioxidants and lidocaine have been used.36,37

**EFFICACY OF MEDICATIONS FOR NEUROPATHIC PAIN**

Most patients with NP do not obtain complete relief of pain with any medication and it is important to advise patients concerning realistic expectations on the outcome of their therapy. Responders are generally considered to be those patients who experience a 30-50% reduction in pain (not complete analgesia). Many of the drugs discussed here have modest effect sizes for pain relief as reported in various studies, and only 50-70% of study patients respond to treatment. In the clinic, with less precision in patient selection,
the response rate is less and the withdrawal from treatment due to adverse effects is greater so the effectiveness of any treatment is less than expected from the results of published studies. Finally, few comparison studies have been performed to compare efficacy of different treatments.

Figure 2 shows the number needed to treat (NNT) for different classes of drugs for NP. This data is based mainly on results of treatment for PDN although a few other studies of patients with painful polyneuropathy of different etiologies were included. As different disorders respond differently to drug treatments, the NNT will likely vary based on the underlying diagnosis. Table 2 shows recent evidence-based guidelines for the treatment of diabetic neuropathy. Table 3 outlines European Federation of Neurological Societies (EFNS) guidelines for the treatment of NP in different disorders with suggestions for first-line and second- or third-line treatments. Table 4 provides an algorithm adapted from Dworkin, et al. for the approach to the treatment of NP, and Tables 5-7 outline the first-, second- and third-line drugs suggested by the same authors for the treatment of NP pain. Table 8 indicates the treatment of central NP. There is some variation in the different sets of guidelines resulting most likely from differences in the rules used by the different authors for evaluating the evidence.

CONCLUSIONS

There are new pharmacological treatments for NP, but success in treating patients in the clinic remains suboptimal. In future development and in treatment of patients, physicians must consider more than simple reduction in pain and must consider QOL, functional limitations, and comorbidities, as well as the magnitude of pain reduction. Finally, more investigation of combination therapy and head-to-head comparisons of different drugs will help select the best therapy for patients.

REFERENCES

INTRODUCTION

Chronic pain is an exceptionally prevalent pathophysiological condition, and, given the high stakes in pain therapy, it is not unexpected that this problem has commanded considerable attention from the biomedical research community. This discussion will address a very specific topic, namely the role that sodium channels play in the detection and conduction of painful stimuli in the peripheral nervous system (PNS) and in the establishment of chronic pain disorders. While recent progress in this field has significant implications for the understanding and treatment for chronic pain, it should be kept in mind that important advances are also being made in other approaches to this subject.

The pain field recently has been transformed by two general findings. First, it has been shown that special types of sodium channels (isoforms) are selectively expressed in peripheral nociceptive pathways. The significance of these findings in turn, implies that improvements in pain therapeutics may be achieved through the development of compounds that specifically inhibit these selectively expressed isoforms. Second, the expression of sodium channels dramatically changes in cases of chronic inflammatory and neuropathic conditions. This finding suggests that sodium channels themselves play a direct role in the establishment of chronic pain states.

SODIUM CHANNEL EXPRESSION AND FUNCTION IN NORMAL PERIPHERAL NOCICEPTIVE PATHWAYS

As the primary molecular moiety responsible for generating the propagating axonal action potential, sodium channels will naturally be involved in conducting information from PNS pain receptors to the central nervous system (CNS). Additionally, there is evidence that sodium channels also play a role in the actual transduction of painful stimuli to electrical impulses at nociceptive receptors themselves.4,6 Naturally, these roles in normal nociception are reflected in the manner in which local anesthetics relieve pain through their sodium channel blocking actions.

SODIUM CHANNELS ARE A DIVERSE FAMILY OF ISOFORMS WITH UNIQUE EXPRESSION PATTERNS AND FUNCTIONS

Early analysis of purified sodium channels showed that the molecular mechanisms for basic sodium channel functions (i.e., sodium selectivity and permeability, voltage-dependent activation and inactivation) were mediated by a single large (~250 kilodalton) polypeptide.2 However, in many tissues this so-called α-polypeptide is often associated with one or more accessory subunits, and these β-subunits appear to play a role in modulating channel function and expression16 and may well play important roles in pain.18 For
simplicity, this paper will focus solely on the role of the major α channel polypeptide to which is now referred to as the sodium channel.

Sodium channel polypeptides are not expressed by a single gene. Rather, recombinant DNA studies (i.e., cDNA and gene cloning) have shown that sodium channels exist in most organisms as multigenic families, the individual gene products of which are known as isoforms. At least nine distinct sodium channel types currently are known to be expressed in mammals (see Table 1).

### Table 1 Mammalian sodium channel isoforms and their known distributions in excitable tissues

<table>
<thead>
<tr>
<th>Isoform (Standard nomenclature)</th>
<th>Other names in literature</th>
<th>Gene name</th>
<th>Typical distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na\textsubscript{v}1.1</td>
<td>Type I</td>
<td>SCN1A</td>
<td>Dendrites</td>
</tr>
<tr>
<td>Na\textsubscript{v}1.2</td>
<td>Type II/IIA</td>
<td>SCN2A</td>
<td>Unmyel. initial segments</td>
</tr>
<tr>
<td>Na\textsubscript{v}1.3</td>
<td>Type III</td>
<td>SCN3A</td>
<td>Early neuronal development</td>
</tr>
<tr>
<td>Na\textsubscript{v}1.4</td>
<td>SkM1, i1</td>
<td>SCN4A</td>
<td>Skeletal muscle (mature)</td>
</tr>
<tr>
<td>Na\textsubscript{v}1.5</td>
<td>H1, SkM2, i2</td>
<td>SCN5A</td>
<td>Heart, Immature Skel. musc.</td>
</tr>
<tr>
<td>Na\textsubscript{v}1.6</td>
<td>Cer3, PN4</td>
<td>SCN8A</td>
<td>Nodes, synapses, dendrites</td>
</tr>
<tr>
<td>Na\textsubscript{v}1.7</td>
<td>PN1, hNE-Na, Nas</td>
<td>SCN9A</td>
<td>Unmyelinated PNS (pain)</td>
</tr>
<tr>
<td>Na\textsubscript{v}1.8</td>
<td>SNS, PN3</td>
<td>SCN10A</td>
<td>Unmyelinated PNS (pain)</td>
</tr>
<tr>
<td>Na\textsubscript{v}1.9</td>
<td>NaN, SNS2</td>
<td>SCN11A</td>
<td>PNS – free nerve endings</td>
</tr>
<tr>
<td>Na\textsubscript{v}2.x</td>
<td>ret1, NaG, atypical</td>
<td>SCN7A</td>
<td>Nonmyelinating Schwann c.</td>
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</tbody>
</table>

The reasons for this ion channel diversity is unknown. Most investigators agree that there are three basic possibilities. 1) Functional variations may exist among isoforms that are needed for excitation differences required by different cell types. For example, fast channel kinetics are suited for the transmission of high frequencies of action potentials in myelinated fibers, while slow kinetic gating of certain isoforms may be required for the long duration action potentials in smooth muscle or cardiac tissue. 2) Amino acid sequence variations may encode signals that allow channel isoforms to be selectively localized to different membrane areas or specializations (e.g., nodes of Ranvier, neuron dendrites, or muscle fiber t-tubules) through interactions with transport, targeting, or clustering molecules. 3) The noncoding region of channel isoform genes may contain unique regulatory elements that would allow cell, tissue, or developmentally-specific expression of a given isoform. For example, the regulation of cardiac function probably requires sodium channel expression to respond to very different processes and factors rather than the development of excitability in the nervous system.

Note that these three different explanations are not exclusive of one another, and there is good evidence that all three explanations of ion channel diversity apply in at least one example. Thus, there are elegant studies that demonstrate the existence of specific gene regulatory elements and transcription factors that control the specific expression of certain sodium channel isoforms, while the selective targeting and clustering of channel isoforms has been shown in a number of studies. It is on this latter phenomenon that this discussion will now focus as background to the exploration of sodium channels and pain.

### Sodium Channel Isoforms Are Selectively Expressed among Excitable Tissues

The most direct way to determine the distribution of various sodium channel isoforms in excitable tissues is to use immunohistochemical methods in which antibodies that are specific for each isoform are employed as isoform markers. We and others have made such antibodies to all isoforms, and we have used confocal immunofluorescence microscopy to visualize the distribution of the various channel types in different tissues (Fig. 1). It can be clearly seen that individual isoforms often are selectively expressed in different excitable tissues. For example, Na\textsubscript{v}1.6 is the dominant isoform expressed at nodes of Ranvier, while Na\textsubscript{v}1.7 is restricted to unmyelinated fibers in the PNS. Alternatively, it is sometimes the case that a given cell type may synthesize two or more different isoforms, but then each is subsequently targeted to a different subcellular domain. For example, in retinal ganglion neurons that form the optic nerve, both Na\textsubscript{v}1.2 and 1.6 isoforms are made, with Na\textsubscript{v}1.2 selectively expressed in the initial unmyelinated segment of the retinal ganglion cell (RGC) axon, while Na\textsubscript{v}1.6 is selectively expressed at nodes of Ranvier within the optic nerve itself.

Na\textsubscript{v}1.7, 1.8, and 1.9 Isoforms Are Selectively Expressed in Peripheral Nervous System Pain Pathways

Using immunocytochemical approaches, it has been discovered that three sodium channel isoforms are selectively expressed in pain-conducting pathways of the PNS. Thus isoforms Na\textsubscript{v}1.7, 1.8, and 1.9 are dominantly localized in peripheral sensory ganglia (dorsal root ganglia [DRG] and trigeminal ganglia [TGG]) to small neuron soma involved in pain transmission (see Fig. 1). Na\textsubscript{v}1.7 itself is strikingly associated with pain pathways, as it is highly expressed in both unmyelinated C-fibers that also contain the neuropeptide substance-P (see Fig. 2) and in free nerve endings in nociceptive receptor fields found in the skin, tooth pulp, and the cornea (see Fig. 3).
Evidence That Peripheral Sodium Channel Isoforms Are Functionally Important for the Detection and Conduction of Painful Stimuli

Indications that specific channel isoforms are involved in chronic pain come from studies in which analgesic drugs were tested for their selectivity to block different sodium channel isoforms. In particular, we have found that certain antiseizure drugs commonly used to treat chronic pain (e.g., carbamazepine) are much more efficacious blockers of Nav1.7 sodium channels than Nav1.2 isoforms (Wang and Levinson, unpublished), the latter of which is not predominantly found in peripheral nociceptive neurons or their processes (e.g., see Fig. 1). Recent studies have attempted to more directly address this point using rodent models in which a given isoform is selectively suppressed using RNA antisense approaches or transgenic knockout mice. In general such studies have shown that alteration of Nav1.7, 1.8, or 1.9 expression leads to reduced sensitivity to chronic pain in either inflammatory or neuropathic pain models.

From a clinical point of view the most compelling evidence for specific involvement of PNS isoforms in pain comes from the studies of human familial pain disorders. In particular, so called gain of function mutations in Na\textsubscript{v}1.7 function recently have been shown to account for several inherited erythromelalgias and paroxysmal extreme pain disorders. In these patients, mutations in Na\textsubscript{v}1.7 affect the voltage-dependence of channel gating such that channels either open more readily in response to depolarizing stimuli or they are less affected by inactivation at resting membrane potentials. In either case, it is thought that nociceptor cell bodies, axons, and/or free nerve endings become highly sensitive to subthreshold stimuli or even become spontaneously active, thus subjecting the patient to a sensation of pain when none exists.
Perhaps even more spectacular are congenital Na\textsubscript{v}1.7 mutations that completely eliminate the sensation of pain in affected individuals.\textsuperscript{3} In such individuals, stimuli such as contact with sharp objects or burning hot materials fail to elicit any painful sensations at all. The mutations responsible for this phenotype also completely eliminate the functionality of the Na\textsubscript{v}1.7 isoform, providing further proof for the essential role of this channel in pain sensation.

ROLES OF SODIUM CHANNELS IN CHRONIC PAIN STATES

Sodium Channels Appear to Play a Role in the Maintenance of Inflammatory Pain States

While abundant evidence discussed above supports the necessary role of the Na\textsubscript{v}1.7 isoform in acute pain sensation, it is not yet certain how sodium channels specifically are involved in the clinically important phenomena of chronic pain. Using a rodent model of inflammatory pain, we and our collaborators previously have observed that induction of peripheral inflammation was followed about 24 hours later by a dramatic increase in the expression of sodium channels in DRG neuron cell bodies.\textsuperscript{11,12} Furthermore, this increase was found to be selective for Na\textsubscript{v}1.7 but not Na\textsubscript{v}1.8.\textsuperscript{12} On this basis we hypothesized that inflammation-induced Na\textsubscript{v}1.7 synthesis was required for the maintenance of the critical features of this form of pain, such as hyperalgesia and allodynia. In particular, it is possible that Na\textsubscript{v}1.7 expression is increased at the wound site and in the surrounding tissues, thus conferring on them a lower threshold to activation by non-noxious stimuli, perhaps accounting partially for the phenomena of allodynia and hyperalgesia.

A Hypothesis of Neuropathic Pain Involving Ectopic Sodium Channel Expression

Neuropathic pain—pain that accompanies nerve injury or other pathological conditions (e.g., diabetic neuropathy, multiple sclerosis)—is thought to originate from different mechanisms than inflammatory pain. In particular, such pain is often characterized by extreme ectopic mechanical sensitivity and by spontaneous painful sensations. In collaboration with colleagues at Louisiana State University Medical Center, we have investigated possible mechanisms for neuropathic pain using tissues excised from human neuromas. A striking finding was that the expression of sodium channels is dramatically elevated in such varicosities, with highly abnormal, extensive large clusters visible (see Fig. 4).\textsuperscript{10} Further, the subjective sensation of preoperative pain from the donor subjects correlated well with the level of increased expression in neuroma tissue as judged by immunoassay. This led to the hypothesis that

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**Figure 2** Selective expression of the Na\textsubscript{v}1.7 isoform in presumptive nociceptive C-fibers. These images were taken from immunostained rat sciatic nerve fibers (40x objective). **Top:** Na\textsubscript{v}1.7 immunofluorescence in unmyelinated fiber bundles. **Bottom:** Substance-P immunoreactivity in same field as top panel. Note the typical punctuate pattern of substance-P immunofluorescence in same fibers that were Na\textsubscript{v}1.7-positive in the top panel. In this panel the brightness has been increased to show the nonspecific autofluorescence in large myelinated fibers that are Na\textsubscript{v}1.7-negative.

**Figure 3** Expression of Na\textsubscript{v}1.7 in tooth pulp, skin, and cornea. In rat tooth pulp, the pattern of Na\textsubscript{v}1.7 immunofluorescence suggests selective localization to fine unmyelinated fibers and free nerve endings in the coronal pulp (60x objective). Similarly, in human skin unmyelinated fiber bundles and presumptive nerve endings are brightly stained for Na\textsubscript{v}1.7. The rat cornea whole mount shows a branching Na\textsubscript{v}1.7-positive nerve bundle overlying the stroma.
increased sodium channel expression in injured nerve segments resulted in a mechanically-sensitive ectopic focus that also generated spontaneous painful impulses.

The Formation and Maintenance of Sodium Channel Clusters Appears to Depend on Signals from Adjacent Myelinating Glia

How might such ectopic sodium channel clusters develop in injured nerve? Clues to this process may be seen in the way that sodium channel clusters are created on myelinated nerve axons. The formation and maintenance of high density sodium channel clusters at nodes of Ranvier in myelinated nerve axons is an example of the selective expression of membrane proteins at extreme distances from their point of synthesis in the neuron soma. Our previous work has shown that such exquisite targeting of channels is largely determined by myelinating glia themselves, i.e., Schwann cells or oligodendrocytes. In early development, myelinating cells apparently induce the formation of high density sodium channel clusters adjacent to their outer margins on the axonal membrane, and, further, these clusters appear to move ahead of the growing glial cell as the myelin wrapping extends along the axon. Stable nodes of Ranvier are then formed when clusters from adjacent myelinating glia approach each other and then fuse into a mature, stable cluster. At present the signaling pathway from myelinating cell to the axon that creates such dense sodium channel clusters is not entirely understood, although it appears to involve interactions of specific membrane receptors on the axon with those of the glial cell.
The Generation of Ectopic Clusters in Injured Nerve May Be Due to Focal Demyelination

What happens in cases of chronic demyelination or failure to form myelin developmentally? With time, as with human neuromas, large numbers of amorphous and enlarged channel clusters appear on the demyelinated axon.5,8,9 This is also true for inflammatory and mechanical injuries in human tooth pulp and in animal models of nerve injury (see Fig. 5).13,14,15

We suggest that such clusters are the source of both ectopic mechanical and spontaneous pain associated with nerve injury. How might such clusters form? We further hypothesize that injury-induced focal demyelination is responsible. In this scheme, chronic loss of myelin results in changes in the signaling process between glia and nerve that maintains well-defined clusters of channels in myelinated fibers. As a result, larger clusters form in the now extended gap between myelin sheaths. Our results show that such abnormalities can occur also on a smaller scale when nodes start to become locally distorted (see Fig. 6); in such cases, nodal clusters first enlarge in the widening gap, then often split into separate clusters. As the gap widens further, we infer that each cluster stays associated with its glial edge to form a “heminode.” Finally, if this demyelinated gap persists long enough, we propose that abnormal, large, amorphous clusters or group of smaller clusters may form in the demyelinated axon. We propose that any or all of such clusters may display spontaneous activity and ectopic sensitivity, thus serving as sources of local chronic pain.

Non-nodal Sodium ChannelIsoforms Are AbnormallyExpressed in Remodeled Clusters in InjuredMyelinatedNerve Fibers

A further finding that may have significance for the generation of painful impulses at nerve injury sites is that non-nodal sodium channel isoforms (i.e., non-Na,1.6 channels) appear to be abundantly expressed in remodeled and newly-appearing clusters in demyelinating areas. Thus both Na,1.7 and 1.8 isoforms populate such clusters, and even are found in some otherwise normal appearing nodes.19 We suggest that such clusters, which probably are comprised of isoform mixtures, will have novel excitability properties that make them more likely to activate spontaneously or upon ectopic stimulation. If so, then more efficacious analgesics for neuropathic pain might be developed if they are targeted to either Na,1.7 or 1.8 isoforms.

Why do non-nodal isoforms appear in myelinated nerve fibers as a result of injury? Our recent work shows that in the postnatal development of PNS myelin in rodents all neuronal sodium channel isoforms (i.e., Na,1.1-1.3, Na,1.6-1.9) initially are expressed when nodes of Ranvier are first formed, but they are gradually eliminated from nodal clusters over a course of about 2 weeks in favor of the uniform expression of Na,1.6. Further, such elimination of non-nodal isoforms is delayed in mutant mice in which the myelination process is delayed. Thus, we propose that the development of compact myelin induces a Na,1.6 selective targeting program in neurons, and that demyelination reverses this process, allowing non-Na,1.6 isoforms to be reexpressed in axons in which significant demyelination has occurred.

APPRAISAL TO ADVANCED PAIN THERAPEUTICS

As noted earlier, the realization that Na,1.7, 1.8, and 1.9 play specific roles in the neurobiology of pain strongly suggests that these isoforms would be excellent targets for new drugs for chronic pain management. A number of groups and companies actively are involved in developing such compounds.

In an alternative approach to this problem, we and collaborators have used gene therapy methods to selectively reduce the expression of Na,1.7 channels in a rodent model of chronic inflammatory pain.24 In our studies, inflammation of rat paws was induced by injection of a noxious substance, and the resulting thermal hyperalgesia and mechanical allodynia was characterized. Na,1.7 expression was then selectively reduced in the DRG neurons innervating the lesion by injecting a recombinant, nonreplicative herpes simplex virus (HSV) expressing Na,1.7 antisense mRNA at the injury site. In these treated animals we found that pain thresholds were significantly elevated compared with control animals injected with nonantisense expressing HSV, and these behavioral changes paralleled reduction in Na,1.7 channel expression as measured by immunofluorescence. Selective reduction of sodium channel isoform expression by gene therapy would appear to be a promising approach to the management of chronic pain.

SUMMARY

Sodium channels appear to play significant roles in the establishment of chronic pain states, in addition to their classical roles in the detection and conduction of acute pain stimuli. The finding that only one or a few sodium channel isoforms are involved in these processes suggests that therapeutic approaches that selectively reduce the function of these isoforms will be an important source of advances in the treatment of chronic pain in the future.

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In the United States alone, almost 20 million people suffer from symptoms of peripheral neuropathy. The estimates are that 3% of the general population will eventually be affected with peripheral neuropathy and that 60% of diabetics will develop some degree of nerve damage. Painful neuropathies are one of the most common complaints that bring patients to neurologists. Unfortunately, in the majority of cases, the cause either remains unknown, or, as in the case of diabetes, there is no effective therapy to cure the underlying pathophysiology. Painful small fiber neuropathies pose an even greater problem with very few reversible causes ever being identified. For these patients the only option is to try to minimize the symptoms resulting from the nerve damage.

While there are several Food and Drug Administration (FDA) approved medications, as well as numerous medications used off label to treat the pain associated with peripheral neuropathies, only 60-70% of patients respond to even the best studied medications. In addition, these symptomatic therapies do not offer the patients the chance to improve the underlying nerve damage. As patients become more educated about their disease management, questions are posed to us as treating physicians about what other options are available for our patients. While traditional medical education ignores or frowns upon alternative therapies, there are several well-studied treatments available for the treatment of painful peripheral neuropathies besides prescription medications. These options include nutritional supplements, topical creams, electrical or infrared light therapies, and even the possibility of surgical approaches.

This discussion will evaluate nonprescription medications and nonconventional therapies for neuropathic pain. Because the number of alternative therapies that claim to have the ability to cure peripheral neuropathies is nearly endless, we will discuss only those treatments which have been studied in randomized placebo-controlled trials or which have become widely used.

**METANX**

There have been numerous studies of individual nutritional supplements in the treatment of patients with painful peripheral neuropathies; however, prior to the 1988 Orphan Drug Amendment, supplements were not FDA approved for medical purposes. In the 1988 Orphan Drug Amendment, the FDA created the designation of a medical food. These are products which are formulated to be consumed or administered under the supervision of a physician and are intended for the specific dietary management of a disease or condition (section 5[b]3 of the Orphan Drug Act (21 USC 360ee[b]3). Medical foods are distinguished from nutritional supplements by being targeted for the distinctive nutritional re-
requirements of specific disease conditions and must be used under a physician’s supervision through a prescription.

Metanx, a nutritional medical food supplement, is the only supplement that is approved by the FDA for the treatment of diabetic peripheral neuropathy. This distinct nutritional supplement was approved for people who presented with loss of protective sensation and neuropathic pain associated with diabetic peripheral neuropathy and or hyperhomocysteinemia who present with lower extremity ulceration. Metanx is a prescription containing the active forms of folic acid, l-methylfolate, vitamin B6, pyridoxal 5'-phosphate, and vitamin B12, methylcobalamin. The use of the active forms of these agents is believed to be important since each person’s ability to absorb and convert other forms may be limited by genetic factors as well as age-related and/or metabolic obstacles.

Metanx offers the possibility of having a positive effect on peripheral nerve function by attempting to correct biochemical abnormalities within the nerve itself. The components within Metanx have been shown to increase vascular flow to the peripheral nerve. Metanx targets the endothelium to improve blood flow by increasing the synthesis of endogenous nitric oxide levels. It has also been shown to improve/restore protective sensation and vibratory sensation in patients with diabetic peripheral neuropathy. A majority of patients demonstrated improved peripheral nerve sensation with subjective improvement in their pain. In a controlled trial of patients with painful diabetic neuropathy, patients receiving Metanx had a 35% reduction in pain compared to only an 11% reduction in patients receiving acetaminophen (p < 0.001).

**ALPHA LIPOIC ACID**

Alpha lipoic acid (ALA) is thought to work as an antioxidant in both water and fatty tissue, which enables it to enter all parts of the nerve cell and protect the cell from damage. It is a potent antioxidant that has been shown to improve endoneurial blood flow and Na+/K+-ATPase activity. The SYDNEY trial found that intravenous ALA rapidly and significantly reduced sensory symptoms and the pain of diabetic neuropathy. In this parallel-group study, 120 metabolically stable diabetic patients with symptomatic (stage 2) diabetic sensorimotor polyneuropathy were randomized to receive intravenous infusions of 600 mg ALA or placebo for 5 days per week for 14 treatments. After 14 treatments, the mean total symptom score improved from baseline by 5.7 points in the ALA group and by 1.8 points in the placebo group (p < 0.001). The ALA group also fared significantly better than the placebo group in terms of improvement on burning pain, numbness and pricking sensations, neuropathy impairment score, and global assessment of efficacy. A second study was then undertaken with ALA using the oral form. This SYDNEY 2 trial demonstrated that oral ALA lessened pain in people with diabetic neuropathy. In this study, 166 people with Type 1 or Type 2 diabetes were divided into four groups. Three of the groups received different doses of ALA, ranging from 600 mg/day to 1800 mg/day, while the fourth group received a placebo. After 5 weeks of once-daily treatment, all three groups that had been taking ALA experienced reductions in total neuropathy symptoms, stabbing pain, and burning pain compared to the placebo group (p < 0.05). There were no differences among the three groups receiving ALA.

Potential side effects of ALA include fatigue and insomnia. These side effects increase as the dose increases. High doses could also potentially lower blood sugar, which is beneficial to patients who have diabetes, but it requires close monitoring of blood sugar levels. ALA may lower levels of thyroid hormone, which should be monitored in anyone taking ALA and thyroid hormone replacement.

**ACETYL-L-CARTININE**

Acetyl-L-Carnitine (ALC) is a nutrient that helps the body turn fat into energy. Studies have shown that people with diabetes have lower levels of ALC. Replacement with oral ALC has been correlated with correcting abnormalities in Na+/K+-ATPase, raising levels of nitric oxide, and improving lipid peroxidation. ALC has been proposed as a treatment for many conditions because of its potential role in reducing oxidative stress.

Preliminary studies in diabetic rats treated with ALC demonstrated that these animals maintained near normal nerve conduction velocities without any adverse effects on glucose, insulin, or free fatty acid levels. These observations led scientists to summarize that ALC can support nerve regeneration after experimental injury and several large studies were carried out in patients with painful diabetic neuropathy. In one study of over 1,000 patients, participants were randomized to either 1500 or 3000 mg/day of acetyl-L-carnitine or a placebo for 52 weeks. There was a significant improvement in Analogue Scale (VAS) pain scores. The 500 mg t.i.d. dose group showed a 22% reduction in pain while the group taking 1000 mg t.i.d. showed a 42% reduction in pain (p = 0.025 and p = 0.024). This study also evaluated patients’ sural nerve biopsies in a subset in each group. After 1 year of therapy, patients taking 500 mg and 1000 mg t.i.d. had sural nerves with significantly more nerve fibers and regenerating clusters than the placebo group (p = 0.027 and p = 0.033). De Grandis studied 1000 mg/day of ALC given intramuscularly for 10 days followed by 2000 mg/day of oral ALC for 1 year in a double-blind, placebo controlled trial. The active arm had a significant improvement in pain scores (p < 0.01) and showed a significant improvement in sural nerve conduction velocity (p < 0.01) and also an increase in peroneal motor amplitude (p < 0.01).

ALC has been shown to have a low toxicity and has been shown to be well tolerated over several studies. Side effects that have been seen include nausea, diarrhea, vomiting, and headaches, but are known to be transient.
NEURO-V

Despite the promising data on the above agents, many physicians have been underwhelmed with the successes seen by prescribing any of these products individually. This raises the possibility that a combination approach could have more clinical benefit. One such product, Neuro-V, is a combination nutritional supplement that contains many of the individual agents shown to have success in treating patient with painful diabetic neuropathy. Neuro-V contains 1 mg of cyanocobalamin, 800 mcg of folic acid, 1500 mg of ALC, 600 mg of ALA, 300 mg of n-acetyl cysteine, 1.5 mg of pyridoxine HCl, and 25 mg of grape seed extract. This unique compound of nutritional supplements was created to alleviate the symptoms seen with painful neuropathies; however, this combination has not been FDA approved. There is a need for a large randomized controlled trial of this or other combination nutritional supplements to see if the effects seen on an individual basis can be magnified. We have been impressed anecdotally that this compound is well tolerated, appears effective, and is cheaper for patients than purchasing the individual components (www.neurovitality.org).

TOPIC AGENTS

Capsaicin and lidocaine are the two main topical agents used for diabetic neuropathy. Capsaicin is an alkaloid derived from chili peppers that works mainly on sensory C fibers to deplete substance P. This causes desensitization to afferent sensory nerves resulting in pain relief. Randomized controlled trials have reported benefit from topical capsaicin 0.075% in patients with post-herpetic neuralgia. A disadvantage to capsaicin use is that it must be applied three to four times daily for up to 8 weeks for optimal pain relief. High-dose capsaicin patches containing 8% synthetic capsaicin can reduce pain in patients with human immunodeficiency virus (HIV)-associated peripheral neuropathy. The patch was only applied for up to 90 minutes before being removed, but the benefits of a single application were seen for up to 12 weeks. Patients receiving the high dose patch often required some immediate rescue medication because of the pain associated from the therapy. Adverse effects include burning, stinging, and erythema.

In contrast to capsaicin, lidocaine works by inhibiting the voltage-gated sodium channels in the damaged nerves. Lidocaine patches have been studied in randomized placebo-controlled trials in post-herpetic neuralgia patients with brush allodynia. There was a statistically significant albeit small benefit to therapy. While case reports have supported the use of lidocaine patches in patients with peripheral neuropathy, no randomized controlled trials have been conducted specifically related to diabetic neuropathy. The most common adverse effect associated with lidocaine use is skin irritation.

There is evidence to suggest that impaired nitric oxide (NO) generation is important in the pathogenesis of diabetic neuropathic pain. Based on this hypothesis, studies to examine the effects of isosorbide dinitrate (ISDN), a NO donor with local vasodilating properties, in spray form in the management of chronic neuropathic pain were conducted. One study was a double-blind, randomized, placebo-controlled, two-period cross-over design that looked at placebo spray versus ISDN for 4 weeks. The study illustrated that ISDN spray reduced overall neuropathic pain (p = 0.02) and burning sensation (p = 0.006); however, no treatment difference was observed with other sensory modalities such as hot/cold sensation, tingling, numbness, and hyperesthesia. At study completion, 11 patients (50%) reported benefit and wished to continue using the ISDN spray, four (18%) preferred the placebo spray, and the remaining seven (32%) were undecided. There were no significant side effects noted in the treatment periods.

FREQUENCY RHYTHMIC ELECTRICAL MODULATION SYSTEM

There have been many studies examining the potential for electrical nerve stimulation to improve the symptoms of diabetic peripheral neuropathy including transcutaneous electrical nerve stimulation (TENS). A novel system has recently been developed that differs from TENS through its use of sequences of automatically modulated electrical stimuli. The hypothesis is that by applying low-level subthreshold electrical stimuli proximal to a motor nerve that one can effect pain modulation, as well as possibly improve nerve function by improving vasomotor activity and angiogenesis. The treatments are delivered for 10 days over a 3-week period with each treatment lasting 30 minutes. Unlike the TENS units, the frequency-modulated electromagnetic stimulation (FREMS) machines are not portable and have to be carried out by health care providers.

Although the studies of FREMS have been small, there are now more than 20 published randomized controlled trials that have demonstrated some efficacy. In one double-blind cross over study of 31 patients with painful diabetic neuropathy, there was a significant reduction in daytime and night-time pain (p < 0.02). There was also a significant increase in motor nerve conduction velocity (p < 0.05) and an improvement in sensory nerve conduction velocity although not statistically different than baseline.

At present, the difficult part of prescribing FREMS therapy is the limited number of places where it is available in the United States and the fact that it has to be administered by some type of health care provider. The side effects are minimal and mainly include a slight burning sensation at the site of electrode placement.

PHOTIC THERAPY

Another form of alternative therapy designed to improve symptoms of peripheral neuropathy involved light therapy. Monochromatic infrared energy (MIRE) has been studied in patients with peripheral neuropathy. This type of therapy is often called anodyne therapy and can be delivered at home or in health care providers offices. This methodology delivers a single wavelength infrared light pulse. This is delivered at 890 nm, outside of the visible spectrum, and penetrates approximately 5 cm into the skin. The light is then absorbed by the red blood cells. The theory is that this pulse causes the release of nitric oxide from the red blood cells. The nitric oxide then serves as a vasodilator which can increase blood flow and reduce pain.
In 2008, a double-blind, sham-controlled study of MIRE therapy was performed and was shown to have no benefit on measures of quality of life, nerve conduction studies, or pain.23

SURGICAL DECOMPRESSION

Surgical decompression at the site of anatomic narrowing has been promoted as an alternative treatment for patients with symptomatic diabetic neuropathy.

Currently, there is not enough evidence to recommend or discourage the use of surgical decompression for treating diabetic neuropathy; however numerous studies by Dr. Lee Dellon have retrospectively analyzed multiple peripheral nerve decompression using a Tinel’s sign as evidence for compression and clinics have been established internationally to perform these types of procedures. As an example, one study of 20 patients (14 type I and 6 type II diabetics) who underwent a total of 31 nerve decompression procedures stated that 79% of the surgically-decompressed nerves improved in their two-point discrimination test postoperatively. None of the decompressed nerves worsened, whereas 32% of the contralateral nontreated nerves worsened in their two-point discrimination (p = 0.001). Twenty-one percent of the surgically treated nerves and 59% of the nonsurgically treated nerves remained unchanged at followup assessment.24

This surgical decompression is based on the hypothesis that diabetic nerves are more vulnerable to compressive injury at potential sites for entrapment. According to this hypothesis, most patients remain asymptomatic despite having diabetic nerve disease. Only when the second pathology occurs (compression of the nerves at entrapment sites) will the patients become symptomatic. Thus it has been hypothesized that symptoms in diabetic sensorimotor neuropathy may be due, in part, to compression of multiple peripheral nerves.25 Although this hypothesis has some experimental support,26 evidence to the contrary shows resistance to axonal degeneration after nerve compression also exists; therefore, there is inadequate data concerning the efficacy of decompressive surgery for the treatment of diabetic neuropathy. There is clearly a need for prospective studies to examine this modality and some of this research is underway.

CONCLUSION

There are a variety of prescription medications available for patients with painful peripheral neuropathies. However many patients remain frustrated with ongoing pain or unwanted side effects from these therapies. Patients have also become more aggressive in seeking out alternative therapies. Therefore, it is more important than ever for us as treating physicians to have at least a basic understanding of what is available in the unconventional realm of alternative therapies and possibly be able to offer some guidance to our patients in terms of treatment which have some basis in science. Hopefully this review will serve as a starting point to make you familiar with some of the better-studied alternative therapies and possibly allow you to integrate some of these modalities into your current practice.

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INTRODUCTION

Pain hugely impacts the individual patient, the family, and society as a whole. It is a highly personal and subjective experience modulated by cognitive, emotional, and environmental factors. During the 1990s, designated the Decade of the Brain, investigators significantly advanced our understanding of the function and structure of the brain through imaging techniques such as functional magnetic resonance imaging (fMRI), voxel-based morphometry (VBM), magnetoencephalography (MEG), single-photon computed tomography (SPECT), and positron-emission tomography (PET). Investigations conducted with these techniques revealed a complex neural matrix—termed the pain matrix—involved in pain processing and perception and laid to rest a previously controversial concept: the involvement of the cerebral cortex in pain processing. Recently, functional neuroimaging has provided us with useful information regarding: 1) brain regions involved in cognitive, affective, and physiological manipulation of pain; 2) neural plasticity associated with neuropathic pain conditions as well as other chronic pain disorders; and 3) the effects of therapeutic agents on central neural systems.

Pain and the Brain: What We Have Learned From Functional Neuroimaging

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INTRODUCTION

Pain has been defined by the International Association for the Study of Pain (IASP) as “an unpleasant sensory or emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” This definition classifies pain as a subjective experience; therefore, unlike the experience of many diseases such as hypertension or diabetes, there is no objective measurement for a patient’s pain. Physicians must do their best to correlate objective data (physical examination findings, imaging results, laboratory tests) with the patient’s subjective reporting. Further complicating the problem is the fact that pain is often confused with the nociception—the neural signals generated and transmitted to the spinal cord and brain in the face of stimuli that are potentially or actually tissue-damaging. Pain, in contrast, requires a functioning brain to process these nociceptive signals and translate them into a subjective experience.

This contrast between nociception and pain is particularly important in chronic pain conditions where there is a lack of objective tissue damage but pain is still present. These neuropathic or non-nociceptive conditions are often the result of dysfunction or damage within the spinal cord, brainstem, or brain. It is this damage to the peripheral and central nervous system (PNS and CNS) that warns us of actual or potential tissue damage. However, with neuropathic pain, these signals have become maladaptive in that they impart no beneficial survival value. Chronic neuropathic pain becomes insidious in that it is often associated with depression, anxiety, decreased libido, altered appetite, and sleep disturbances.

NOCICEPTION VERSUS PAIN

FUNCTIONAL NEUROIMAGING AND THE BRAIN REGIONS INVOLVED IN PAIN
invasive imaging technologies has made the human CNS available for direct examination and comparison between healthy subjects and chronic pain patients. This allows for confirmation and the extension of the wealth of knowledge about basic nociceptive processing and plasticity, learned from animal research, and translate it more confidently to humans.

Neuroimaging studies have helped identify and characterize brain structures involved in the recently described “pain matrix.”2,3 The pain matrix is thought to consist of at least two main systems working in parallel: the lateral and the medial pain systems.3 The lateral system, primarily composed of the primary and secondary somatosensory cortices (S1, S2), is responsible for the sensory-discriminative components of pain. In contrast, the medial system, consisting of brain regions including the anterior cingulate cortex (ACC), insular cortex (IC), prefrontal cortex (PFC), basal ganglia, and periaqueductal gray (PAG), is primarily responsible for the affective, motivational, attentional, and evaluative components of pain. The lateral and medial pain systems overlap significantly with each other and other pain matrix areas—supplementary motor area, premotor cortex, parietal cortex, and hypothalamus. These areas are potential targets for therapeutic interventions and a better understanding of the mechanisms linking cognition, emotion, and pain.

In addition to identifying regions classically thought of as being in the pain matrix, neuroimaging techniques have discovered numerous brain regions and subregions not previously implicated that play unique roles in the processing and perception of pain. As such, the imaging research shows that while the traditional pain matrix definition remains valuable, it is in some respects outdated. For example, more essential role played in pain by such traditional matrix definition remains valuable, it is in some respects outdated. Neuroimaging elucidates the reality that the regions are complex and each region contributes uniquely to the experience of pain, neuroimaging elucidates the reality that the regions are complex and overlapping in their functions with other cognitive and emotional experiences.

**EMOTIONAL AND COGNITIVE INFLUENCES ON PAIN**

Pain's intensity and unpleasantness correlate well with levels of noxious stimulation. The pain experience, however, can be significantly modulated by thoughts and feelings. Neuroimaging has helped elucidate many of the neural correlates regarding factors well known to modulate the experience of pain, including attention,4 anticipation,5 placebo,6 empathy,7,8 and fear/anxiety.9 Each factor impacts how humans perceive pain, and an increasing number of functional neuroimaging studies are investigating how these factors affect pain perception and activity in the brain.

**Effects of Attention on Pain**

There have been anecdotal reports for centuries of people who suffer traumatic injuries and yet experience little or no pain. Furthermore, it is well-established that distraction from a noxious stimulus results in a decreased perception of pain.10 Many chronic pain patients use distraction in its many forms to manage their pain: walking the dog, listening to music, reading a book, and working are just some examples. Attention to a different task or cognitive distraction attenuates activity in the ACC, insular cortex, thalamus, somatosensory regions, and the PAG.11

Attention to pain, however, has produced varied results, sometimes enhancing pain perception and sometimes reducing it. The variability may be gender-related and potentially due to differences between normal subject populations and pain patients.

The neural correlates responsible for attentional modulation of pain are not known. Data suggest multiple levels of the CNS are involved. One such system is the opiate-sensitive descending and ascending pathways: a pathway from the frontal cortex to the amygdala, PAG matter, rostral ventral medulla, and finally the dorsal horn of the spinal cord, as well as ascending pathways through the medial thalamus to the ACC.12

Although data is limited, studies have demonstrated that patients with chronic pain have impaired ability to distract themselves from their chronic pain, independent of their pain intensity. These studies strongly suggest cortical and/or subcortical dysfunction as a cause for this impairment. Probable areas involved in this dysfunction include the orbitofrontal cortex and ACC. Recently, Apkarian used another method of neuroimaging—volumetric brain morphometry—to characterize changes in anatomical gray and white matter in patients with chronic back pain. He found that these patients showed 5-11% less gray matter, particularly in the prefrontal cortical regions, an area strongly associated with attentional modulation. This loss was equivalent to 10-20 years of normal aging.18

**Effects of Anticipation, Fear, and Anxiety on Pain**

Expectation and anticipation of pain are known to influence the immediate unpleasantness of pain. Uncertain pain has been demonstrated to increase unpleasantness and to result in less pain tolerance compared with certain pain. There is also evidence in humans that acute stress can activate the pain-modulating circuit that contributes to analgesia. This analgesia may be achieved by the stress-regulatory systems including endocrine, autonomic, immune, and opioid systems. Recently, a small number of studies examined the neural mechanism underlying the anticipation of pain. Expectation of pain activated the neighbor medial frontal lobe, insular cortex, and cerebellum, but expectation did not activate locations mediating pain experience itself.15 More recently, investigators found that most brain systems associated with pain processing can be activated by anticipation of a painful stimulus; however, the anticipatory responses are smaller than the pain intensity-related responses.16
Effects of Mood on Pain

Mood and emotion have also been shown to alter pain perception, although the difficulty in dissociating mood and attention may have confounded previous reports. Manipulations positively affecting mood or emotion such as soothing music, pleasant pictures, and humorous films, generally reduce pain perception. However, manipulations negatively affecting mood or emotion have not always been consistent.

Recent research indicates that people who fear pain tend to report more negative pain experiences. Those with a high fear exhibited a selective attentional bias towards pain-related information, compared to those classified as low in their fear of pain. The author’s laboratory recently investigated the effects of fear and anxiety related to painful sensations as a means of explaining individual differences in pain perception. They identified that fear of pain correlated strongly with lateral orbitofrontal brain activation—a region associated with response regulation. Anxiety related to pain correlated with medial prefrontal activation—a region associated with self-focused attention. They believe that these psychological factors may play a significant role in explaining the differences in pain perception related to emotion.

Results from studies on the attentional, anticipatory, and other cognitive modulations of pain, combined with biochemical and anatomical understandings of analgesia, provide us with insights into the top-down and bottom-up plastic changes that occur in the CNS. Functional neuroimaging research in this area has just begun, concentrating on the interplay between affect and pain perception. Future research using functional neuroimaging is likely to have a significant impact on cognitive and other therapeutic interventions.

NEUROIMAGING CHRONIC PAIN STATES

In contrast to what is known about acute pain, evidence about the generation and maintenance of chronic pain suggests that changes in central pain processing are mediated through mechanisms of neural plasticity, ultimately leading to hyperexcitability of central structures. It has been thought for many years that the processes of acute and chronic pain are very distinct, involving different pain systems (i.e., the medial system with chronic pain and lateral system with acute pain). So far, functional neuroimaging studies provide little evidence that acute pain and chronic pain are processed within different parts of the pain matrix. Neuroimaging studies in patients with peripheral or central nerve lesions have also implicated similar brain structures activated during experimental acute pain. Peripheral nerve lesions (compression, nerve section, or amputation) often lead to spontaneous neuropathic pain in the involved area. Imaging studies have demonstrated a decrease in regional cerebral blood flow in the contralateral thalamus in patients with neuropathic pain. Interestingly, deep-brain stimulation of the contralateral thalamus in patients with neuropathic pain has been shown to provide symptomatic relief with accompanying increase in regional cerebral blood flow (rCBF) in this area as well as in S1 and insular cortex. Additionally, changes in the somatotopy of the primary sensory cortex have been shown to occur in amputees and have correlated with their experience of phantom pain; similar findings have been found in low-back pain (LBP) patients.

Recent neuroimaging studies have identified abnormalities within the pain matrix in patients with fibromyalgia (FM). A consistent finding in the literature is that FM patients show greater activity in pain-processing structures when intensity of mechanical pressure stimulus is controlled. Areas of greater activation in response to a low-stimulus pressure in FM patients include contralateral S1, inferior parietal lobule, IC, ACC, posterior cingulate cortex (PCC), ipsilateral S2, bilateral superior temporal gyrus, and cerebellum. The findings suggest that individuals with FM experience centrally-augmented pain processing. Similar findings were obtained when a thermal stimulus was used.

While fMRI provides important functional activation information, structural imaging techniques also provide unique, mechanistic information about healthy and diseased CNS processes. VBM, a structural MRI technique that involves morphometric analysis on a voxel-by-voxel basis, is used to quantify the density of gray and white brain matter. VBM has been widely used in psychology and psychiatry to yield novel insights into the mechanisms of Alzheimer’s disease, panic disorder, schizophrenia, and bipolar disorder. VBM has recently been used to detect changes within patients with LBP, cluster headache, and most recently FM. A small, preliminary study found that the FM patients had decreased gray matter in the ACC, IC, medial frontal cortices, and parahippocampal gyri. Notably, these areas overlap heavily with abnormal functional activity identified in other studies and in other pain conditions. The author’s laboratory also has recently identified abnormalities in trigeminal and cortical gray matter distributions in patients with temporomandibular disorder.

Magnetic resonance spectroscopy (MRS) makes it possible to directly investigate tissue metabolism and biochemistry. Recently, investigators demonstrated differences in N-Acetyl aspartate (NAA) concentration in patients with chronic LBP compared with control subjects, anxiety levels (high versus low) and brain regions (dorsolateral PFC [DLPFC], orbitofrontal cortex [OFC], thalamus, cingulate), resulting in a three-way interaction. They found a precise relationship between perception and brain chemistry in that sensory versus affective pain was represented best in the DLPFC and OFC in chronic LBP patients, high versus low anxiety in OFC in normal subjects, and all four regions in chronic LBP patients, and the affective component of pain in the cingulate. It is expected that as the spatial and temporal resolution and the number of substances increase, this technique will become more prevalent on its own or in combination with other neuroimaging techniques with better spatial and temporal resolution.

The neuroimaging of the brain in patients with chronic pain is still in its infancy. The preliminary data support the notion that persistent chronic pain states involve functional abnormalities in the cortical and subcortical areas activated by noxious experimental stimuli in normal subjects.
FUTURE FUNCTIONAL NEUROIMAGING STUDIES OF PAIN IN HUMANS

Advances in functional neuroimaging promise unprecedented explorations of the neural mechanisms underlying pain, including being able to link decades of research in animal models to clinical practice. While the field of functional neuroimaging is coming of age, there are still many obstacles to overcome. For instance, many key regions of the pain matrix are subcortical regions, or they lie at the spinal cord level. These regions may involve small volumes difficult to investigate with current functional neuroimaging technology because of what is being measured (e.g., fMRI measures blood oxygenation and flow, electroencephalography [EEG] measures extracellular current, and magnetoencephalography [MEG] measures intracellular current). Furthermore, there are significant limitations in spatial resolution (e.g., PET, MRS) and in source localization (e.g., EEG, MEG). Studies using multimodal imaging may help overcome these obstacles. Studies of anatomical and functional connectivity—the neural circuitry involved in pain perception and the cognitive and affective factors modulate pain—may provide converging evidence. For example, diffusion tensor imaging (DTI) noninvasively provides microscopic structural information of oriented tissue in vivo. White matter tract structure measured by water proton, anisotropic diffusion is highly sensitive to subtle changes and is being used in studies of cognition, mood, other various disorders, and most recently pain.21,22

While functional connectivity can be studied using fMRI, EEG, and MEG, issues related to signal detection and statistical inference remain. In addition, imaging techniques such as MEG are a valuable tool to measure the temporal relationship between brain regions. PET and MRS are also valuable in identifying the metabolism and specific neurotransmitters involved in pain processing. The advent of real-time fMRI is another exciting tool that may be useful in the studies of pain. Recently, the author’s laboratory studied chronic pain patients and healthy individuals by externally applying pain to elucidate whether one can learn to modulate the perception of pain using feedback of blood oxygenation dependent contrast (BOLD) fMRI signals of brain regions related to pain in real time.20 This technique not only provides causal evidence between certain brain regions and the perception of pain but it also may have therapeutic potential. These directions will further shape our understanding of pain perception, and they may be useful in assessing or developing new or existing treatments.

CONCLUSION

Pain remains a serious health care problem, affecting millions of individuals, costing billions of dollars, and causing an immeasurable amount of human suffering. In designing improved therapies, there is still much to learn about peripheral nociceptors, nerves, spinal cord, and brainstem modulatory systems. However, it is the brain that provides an incredible opportunity to finally understand the experience of pain. Functional neuroimaging is helping unlock the secrets of the sensory and emotional components of pain and its autonomic responses. These techniques are helping physicians and researchers to understand that pain is not a static disease with the pathology localized to the periphery, but instead a highly plastic condition affecting multiple central neural systems. Functional neuroimaging is transforming the understanding of the neurobiology of pain, and it will be instrumental in helping the design of more rational treatments ultimately aimed at reducing pain’s impact on patients.

REFERENCES


Pain management is ubiquitous in all fields of medicine and, in the last decade, has developed into its own subspecialty. Both patients and society as a whole have exerted immense pressure on pain physicians to treat pain aggressively. This insistence for improved pain management in medicine has incited calls for improved training in all Accreditation Council for Graduate Medical Education (ACGME) specialties and consideration for expanded specialty training or the development of a primary pain medicine residency program. Regardless of the method of training, the additional burden is to provide care that is less art and more science, supported by controlled trials to demonstrate indications to ensure effectiveness. The impetus for improved pain management covers all treatment types—medications, physical therapies, interventions, and surgery—and is in concert with a rising demand for services. There has been an explosion in spine procedures performed, with epidural injections and facet injections of the lumbosacral spine being the most common. The Centers for Medicare and Medicaid Services data from 1997-2006 shows that these procedures have increased by over 100% per 100,000 persons with procedures done by general practitioners (23% yearly growth) outpacing those done by pain specialists (12.2% yearly growth). The exponential growth is greatest in the Southeast and for facet injections (60% yearly growth), the procedure for which there is the poorest evidence of effectiveness. In that 10-year period, the percentage of patients over the age of 65 increased by 6.3% (U.S. population increased 11.8%). Lumbar caudal and interlaminar procedures still represent greater than 50% of the total, although the rate of transforaminal procedures is increasing more rapidly. Considerations made for controlling payments include accreditation of locations and practitioners, limiting payment to fluoroscopic procedures, and stronger medical necessity indications. The rationale for stronger medical necessity indications is supported by the finding that in Medicare diagnoses, the primary diagnoses for epidural steroid injections were radiculopathy (40%), axial back pain (36%), and spinal stenosis (23%). Cost-controlling strategies through decreased reimbursement for all services (procedures and evaluation/management) has been somewhat effective in controlling costs as the 11.6% increase in low back pain incidence explains to a large extent the increase in healthcare expenditures spent to treat this disorder in the last 10 years.

The purported goals of spine procedures are two-fold. First, studies have attempted to use medial branch nerve blocks, provocative discography, and sacroiliac (SI) joint injections to distinguish the cause of chronic low back pain. The results of one study showed that the facet joint is the most common pain generator in chronic low back pain with identification of the facet joint in 40% (95% confidence level, 31-49%) of patients, followed by the disc in 26% (95% confidence level, 18-34%) of patients, and the SI joint in only 2% of the patients. However, a more recent analysis reported that 39% (95% confidence interval, 30-50%) of low back pain cases can be accurately diagnosed as discogenic-, SI-, or facet joint-mediated pain. The wide variance in these findings without a clear methodological explanation leads to doubt about the efficacy of these techniques as a diagnosis tool in spite of the logic of this premise.
However, a trial of 101 patients with low back pain evaluated prospectively with SI blocks, discography, and facet blocks was conducted. The SI joint was examined using pain provocation tests, including distraction, compression, sacral thrust, thigh thrust, and Gaenslen’s test (pelvic torsion). Significant relationships (p < 0.05) were found between discogenic pain and centralization of pain during repeated movement testing (guided flexion, extension, lateral bending, and rotation) and pain when rising from sitting. Lumbar facet joint pain was associated with absence of pain when rising from sitting. SI joint pain was related to three or more positive pain provocation tests, pain when rising from sitting, unilateral pain, and absence of lumbar pain. Patients with SI joint pain rarely had pain at or above the level of the L5 spinous process. In contrast, 80% of those with discogenic pain reported midline lumbar pain. Positive relationships were noted for unilateral pain (p < 0.05), pain produced or increased when rising from sitting (p < 0.02), and the presence of three or more positive SI joint pain provocation tests (p < 0.001). Although no test or series of tests were definitive, these significant relationships point to the fact that there are meaningful relationships between physical examination findings, diagnostic injections, and patients subjective symptoms.

The rest of this discussion is divided into the specific spine procedures and their relative success as a diagnostic tool and its second purpose, that as a therapeutic intervention. With regard to this second purpose, the role as a therapeutic intervention has several considerates. First, it must be an intervention with a risk profile favorable for the problem for which it is being used. In addition, it must be an intervention with adequate pain relief to allow return to activity and rehabilitation that is beyond what can be expected from placebo effect. And, third, it needs to provide pain relief that is long enough to be considered a reasonable treatment as a stand alone therapy or to allow for rehabilitation to allow completion of the treatment program.

Every current systematic review on this topic reports that a limitation of any analysis like this is the lack of adequate controlled trials for most every topic that this discussion covers. With this as a noted limitation/weakness, the analysis here attempts to uncover bits of information in each individual paper that might bring some valuable insight into this topic. However, in reviewing the individual trials, common limitations exist. First, the use of sedation or the degree of sedation used is rarely discussed. This makes it difficult to evaluate the utility of a diagnostic procedure. The use of sedation alone results in up to 10% of patients reporting marked reduction in their activity-related back pain. The criteria for a positive diagnostic block vary with papers. Some use a threshold of greater than 50% pain decrease, an amount that may not be different than that expected by a placebo effect. Others use a threshold of 70-80%. Many studies show a marked decrease in the numbers of patients that respond to a second block, indicative of the power of the placebo effect. The results from trials with different thresholds are not comparable and may impact the effect of treatment therapies (e.g., other injections, ablations, surgery).

THE SACROILIAC JOINT

The Evidence of Sacroiliac Joint Injections as a Diagnostic Tool is 2-1, Recommendation Category B

The role of the SI joint as a pain generator has carried with it some controversy. There is little disagreement of the role of the SI joint as a pain generator in spondyloarthropathies. However, an understanding and agreement of the SI joint as a pain generator in degenerative and mechanical back pain is lacking. It has complex innervations from anterior and posterior rami of L2-S3, although the posterior ligament structures have innervations from the lateral branches of the posterior primary rami of L4-S3.

Stimulation pain map studies of 10 healthy volunteers showed an area of unilateral low back pain 3 cm below the posterior superior iliac spine. When applied to a group of 54 patients with low back pain, 16 met these criteria. Ten of 16 had a greater than 50% improvement with intra-articular SI blocks.

An additional limitation of the SI joint block literature is that the clinical evaluation of the SI joint has limited sensitivity, specificity, or inter-rater reliability. In a study of 101 asymptomatic persons, the false-positive rate for the Gillett’s test was 16%; for standing flexion, 13%; and for seated flexion, 8%. However, in men the rates were 4.2%, 10.2%, and 8.3%, respectively, while in women the rates were 26.4%, 17%, and 17.5%, respectively.

In another study using multiple therapist evaluators, the standing stork test was evaluated using a 2-point scale or a 3-point scale. Using a 2-point scale (positive if the pelvis remained neutral or moved caudad), inter-observer agreement exceeded 90% while a 3-point scale (cephalad, caudal, or neutral) was just below 80%. This would indicate that the more gross the measure, the better the agreement. This was true regardless of the sex of the subject, duration of pain, severity of pain, or the side examined.

To overcome this problem, studies have pointed to the importance of combining SI joint evaluations to improve specificity. A blinded evaluation of 48 patients with axial back pain confirmed with SI pain by way of diagnostic blocks. All patients with a positive response to diagnostic injection (80% improved) reported pain with at least one SI joint test. Sensitivity and specificity for three or more of six positive SI joint tests were 94% and 78%, respectively. Tests performed included SI joint distraction, thigh thrust, Gaenslen’s, compression, and sacral thrust. Another study looked at 60 patients with low back pain. Twenty-seven patients responded positively to SI blocks with at least a 50% reduction in pain. An evaluation of multiple SI joint maneuvers including Patrick’s test, Gaenslen’s, SI joint distraction, thigh thrust, and compression was made. Of the 27 responders, 23 were found positive after the multitest regimen and four were negative. For the nonresponders (n = 33), seven were positive and 26 were negative. The calculated sensitivity and specificity of the multi-test regimen were 85% (confidence interval 72-99%) and 79% (confidence interval 65-93%). Positive and negative predictive values were 77% (62-92%) and 87% (74-99%).
A systematic review using the double infiltration technique as a reference test shows that the pooled data of the thigh thrust test, the SI joint compression test, and three or more positive stressing tests showed discriminative power for diagnosing SI joint pain.15

In summary, accumulating data show that SI joint physical examination testing can be useful and effective when multiple examination tests are correlated. Response to SI joint injection similarly correlates to positive SI joint physical examination testing.

The Evidence for Sacroiliac Joint Injections for the Treatment of Axial Back Pain is 2-3, Recommendation Category B

The clinical trials of SI joint injections for the treatment of axial back pain have high variability, leading to decreased certainty in the utility of the procedure. In addition, many of them are retrospective, leaving doubt as to the methodology. One study was completed with 120 patients with axial back pain who did not respond to treatment for a disc herniation noted on magnetic resonance imaging (MRI) scan. At 3 months after SI joint injection, 12.5% had a greater than 50% drop in their pain severity score.16 In another study of 31 patients with a greater than 80% improvement in diagnostic blocks, an improvement of pain severity by 3.2/10 with improved function and work capacity without a decrease in narcotic pain usage was noted.17 Another retrospective study of 50 patients showed that 36.4% had improved pain severity scores of at least 50%, with patients on disability and with pain on lateral bending to the same side not showing improvement.18

Another trial of 25 patients reported that peri-articular blocks were more successful than intra-articular blocks (see Fig. 1), although these results have not been reproduced. The criteria for inclusion were pain location, one positive provocation test, and no hip pain or radicular pain. These injections were performed with lidocaine only.19 The theory for this is that intra-articular injections anesthetize the synovium but do not anesthetize the interosseous or dorsal SI ligaments.20 This throws further confusion into the literature on the effectiveness and appropriateness of intra-articular SI blocks.

A retrospective review, without a control group, of the 67% of 39 patients who showed a greater than 75% improvement of pain on two occasions with local anesthetic were treated with intra-articular steroids. Patients that improved at least 50% in pain severity did so for at least 37 weeks compared with failures who only improved for 4 weeks. Failures were more likely to have a history of lumbosacral fusion.21

The Evidence for Lumbosacral Dorsal Rami Blocks and Radiofrequency Ablation for the Treatment of Axial Back Pain is 2-1, Recommendation Category B

Controversy exists due to a single cadaver study that attempted to evaluate the site for lateral branch blocks (LBBs). This study looked at the depth of L5-S3 lateral branches and noted that some run across the surface of the sacrum while others run more superficially between layers of the dorsal SI ligament. No mention in the study is made if more proximal injection at the exit of the dorsal ramus at the foramen would overcome this problem. Only 36% of lateral branches were stained in the single depth injections while 91% were stained in the multi-depth procedure. Adapting this finding to 10 live control subjects, single depth blocks anesthetized the joint in only 20% while multidepth blocks was effective in 70%. This study has not been duplicated.20

However, a randomized placebo controlled trial of 28 patients using L4-S3 dorsal rami and lateral branch radiofrequency with a cooling probe or a sham ablation technique in patients with greater than 75% improvement with intra-articular injection and LBBs was...
completed. The 1-/3-/6-/12-month improvement of greater than
50% pain level was 79%/64%/57%/14% compared to the placebo
group that showed 14% improvement at 1 month and none
thereafter. The crossover group that received the sham procedure
showed improvement at 1/3/6 months of 64%/55%/36%.22 A ret-
rospective study was also completed of 77 patients who responded
with pain severity decrease of at least 50% with one SI block and
24 with LBBs of L4-S3. The result is that 52% had a greater than
50% pain decrease for at least 6 months with radiofrequency abla-
tion, seeing at least a 3-point drop in a 0-10 point pain severity
score. The patients least likely to improve included those with the
highest pain scores, older patients, and patients with pain below
the knee. Patients who had pulsed radiofrequency fared better than
those with conventional high temperature ablation stratifying for
pain severity and duration.23 This raises the possibility that high
temperature ablation results in denervation of the multifidus, an
important muscle for segment stability. However, this theory has
not yet been assessed.

A prospective trial of 52 patients with SI joint pain that dem-
onstrated greater than 75% improvement to each of two intra-
articular joint injections was conducted of pulsed radiofrequency
ablation. Only 16 had greater than 50% pain reduction in an
ablation of the L4-S3 lateral branches with only a quarter of these
lasting as long as 2 months.24

THE FACET JOINT

The Evidence of Facet Joint Injections as a Diagnostic Tool is 3,
Recommendation Category B

There is far less literature on the physical examination of facet-
mediated pain than there is for SI joint disorders. One study
looking at the clinical factors associated with response to cervical
medial branch radiofrequency ablation showed that a positive re-
response was associated with unilateral paraspinal tenderness. There
was no relationship to pain on extension and rotation, response
to medial branch blocks, history of prior cervical surgery, or facet
joint changes on MRI.25 So, what is being treated? Is it facet pain,
multifidus pain, paraspinal pain, or some other structure? Similar
findings were noted in a study looking at factors associated with
response to cervical medial branch blocks. Only 14 of 33 patients
with unilateral neck pain and a positive response to cervical medial
branch blocks had facet joint tenderness by pressure algometry.26
These studies generate much doubt on the relationship between
cervical medial branch block and facet mediated pain.

An observational study of 152 patients who responded to lidocaine
and bupivacaine intra-articular facet injections was conducted. The
number of patients whose diagnosis changed was nine at 1 year and
16 at 2 years, providing some stability in the diagnosis over time.27

A retrospective study of 282 patients with prior lumbar surgery
demonstrated that 16% responded to intra-articular facet blocks.28
However, no gold standard other than the response to lidocaine in
the facet joint was noted. The false-positive rate of a single facet
block was 49%.

The Evidence for Facet Joint Injections for the Treatment of
Axial Back Pain Due to Spondylosis is 2-3, Recommendation
Category B (see Fig. 2)

In a retrospective study of 438 patients with at least 6 months of
axial neck or back pain, facet blocks were completed to study the
incidence of facet-mediated pain. A positive response was defined as
a greater than 80% pain relief from lidocaine and a longer response
to bupivacaine. The prevalence of persons that met these criteria in
the cervical spine was 39% (confidence interval 32-45%), thoracic
spine 34% (confidence interval 22-47%) and lumbar spine 27%
(confidence interval 22-33%). However, the false-positive rate of a
single block was 42-45% in all regions.29

Figure 2 Cervical facet blocks, lateral view

A double-blinded, randomized, controlled study of 89 patients with
chronic unilateral shoulder pain due to myofascial trigger points in
the upper trapezius muscle received either a C4-C5 intra-articular
facet joint injection or a unilateral multifidis muscle injection. Half
of the patients in the experimental group, but none of the control
patients, reported being completely pain free 1 month after the
injection. The decrease in the pain intensity and the increase in
pressure pain threshold were significantly more in the experimental
group than in the control group over 1 month.30

Pilot trials of intra-articular hyaluronic acid injections have been
reported. A prospective uncontrolled study of 15 patients with
a mean age of 57 with back pain of at least 24 months duration
who responded to local lidocaine injection at one facet joint was
conducted in which they were treated with up to three times with
1 cc of intra-articular hylan G-F 20 injections given 10 days apart.
Statistically significant improvement in pain severity (average,
standing, and walking), Oswestry Disability Index, and sitting
tolerance were noted for 6 months but not for 12 months. No
improvement in standing or walking tolerance was achieved ($p = 0.085$). Patient satisfaction increased from baseline (0%) to 7-10 days (64%) but declined over time (36% at 12 months). Analgesic usage decreased over 6 months ($p = 0.025$). These results had not been observed by prior trials where the inclusion criteria were more relaxed and only a single injection was performed.32

The Evidence for Lumbosacral Medial Branch and Dorsal Rami Blocks and Radiofrequency Ablation for the Treatment of Axial Back Pain is 2-3, Recommendation Category B (see Fig. 3)

A retrospective study looked at the relationship between physical examination and radiological findings (disc degeneration, lumbar stenosis, and facet hypertrophy, as graded by a radiologist) and response to lumbar medial branch radiofrequency ablation. Seventy-seven patients with a greater than 50% decrease in pain severity with medial branch blocks were treated. Only 28 had a positive response. Patients with central or foraminal spinal stenosis had statistically significant correlation with positive outcome of radiofrequency ablation ($p = 0.02$), but not with medial branch block ($p = 0.08$). The presence of facet joint degeneration or hypertrophy was positively correlated with response to medial branch block (71% versus 51%; $p = 0.04$), but not radiofrequency ablation. Not unsurprisingly, disc degeneration did not relate to response to medial branch blocks or radiofrequency.33

A systematic review of the treatment of facet-mediated pain raises most of the major issues concerning radiofrequency ablation for facet-mediated pain. There is a paucity of studies and a near absence of quality studies on this topic. Studies that use 50% of pain as cutoff are too close to the placebo effect to be meaningful. Facet block injection sometimes leads to epidural flow, adding an additional layer of uncertainty to what is being treated. The studies of medial branch blocks have no control group, resulting in little foundation for the premise for the radiofrequency ablation studies. In addition, the medial branch innervates structures other than the facet joint which could be the pain generator. The studies of radiofrequency ablation that show a length of benefit of 4 weeks does not really make sense based on the purported pathophysiology. Some studies indicate that medial branch blocks last longer than radiofrequency; is an ablative technique that denervates the multifidus actually harmful?34

One prospective study provided patients with suspected facet mediated pain with multiple (one to five) medial branch blocks over a year. This resulted in greater than 80% of patients achieving a greater than 50% reduction in pain and a decrease in their Oswestry Disability Index scores of 40%. Their pain severity scores dropped from 8.2 to 3.8/3.6/3.7 at 3/6/12 months. No additional benefit was seen in those patients who had steroid or Sarapin added to the anesthetic. The average time of improvement, in weeks, for subsequent injections was $25 \pm 23.3, 20 \pm 10.5, 14 \pm 4.3, 12 \pm 1.1$, and $10 \pm 0.4$ (overall $15 \pm 9.9$). There was no control group in this study. Half of the patients were disabled at the study onset and there was no change in this status. There was no change in employment or opioid use over time. The large change in pain severity score with no improvement in disability or opioid use was not explained.35

One randomized controlled trial of radiofrequency ablation versus sham ablation in 40 patients with axial back pain of at least 2 years duration with a greater than 80% decrease in pain transiently after medial branch blocks was conducted. Pain severity score improved 1.9/10 in the treatment group compared to 0.4/10 in the sham group. However, the sham group had much lower initial pain scores (4.35 versus 6.03). Improvement in back pain was 2.1 in the treatment group and 0.7 in the sham group, different at a $p = 0.08$.36

One retrospective study looked at 174 out of 209 patients who completed a study of response to lumbar medial branch radiofre-
frequency ablation. In this study, 55 (31.6%) experienced no benefit from the procedure. One hundred and nineteen patients (68.4%) had greater than 50% pain relief lasting from 6 to 12 months and 36 (42.8%) for 12-24 months. Another retrospective study of lumbar radiofrequency ablation looked to see if there was any difference in the outcome of people who had experienced a greater than 50% versus a greater than 80% pain relief with medial branch blocks. Their findings noted no difference between the groups with 52-56% experiencing a greater than 50% improvement in pain scores.

Another retrospective study looked at patients with chronic neck and lumbar pain who had a 50% improvement with facet injections. There were 63 low back patients of whom 27 had prior surgery and 51 neck pain patients. Forty-six of the 114 did not respond to pulsed radiofrequency ablation. Those that did respond noted improvement for 3.93 ± 1.86 months.

CERVICAL AND LUMBAR RADICULAR PAIN

Radicular pain is pain that is in the distribution of the affected nerve root. Therefore, the neurological examination is a critical source of information by which to discover the offending nerve root. However, often there is no frank reflex, motor, or sensory change by which to guide the clinician, and no change in electrodiagnostic studies to help. In this circumstance, it is certainly still possible for the nerve root to sustain inflammation or compression that leads to symptoms. It is also possible that the offending pain generator is a source of referred pain that mimics radicular pain including the facet joint, SI joint, or the hip joint. Physical examination and diagnostic blocks may or may not help to clarify. It is also possible that some structure other than a disc is causing nerve root impingement. Facet joint pathology with hypertrophy or a synovial cyst may cause radicular pain. SI joint injury with anterior capsule rupture can cause irritation to the lumbosacral plexus and mimic radicular pain. And there is always thoracic outlet and piriformis syndrome to consider.

This section will review studies that have explored means to evaluate and treat radicular pain.

One issue that has been discussed in the literature is safety of some of the used techniques. There have been a number of catastrophic outcomes after cervical transforaminal epidural injection (see Fig. 4). A survey showed 30 brain and spinal cord infarcts in the literature with at least 13 fatalities. However, due to the medicolegal cases pending, exact detail on the technique used in these injections is not known, although all cases used particulate rather than soluble steroids. It is uncertain if the procedure is unsafe, if the techniques used were not maximally careful, or if frank negligence was at play.

A randomized trial of 30 patients receiving cervical transforaminal epidural steroid injections compared dexamethasone and triamcinolone. At 4 weeks, the dexamethasone group had a 48/100 drop in pain severity to 29 at 4 weeks compared to a 49/100 drop to 17 in the triamcinolone group. There were no statistically significant differences in the groups although the dexamethasone group had more patients with no response and more with 100% relief. This would indicate the relative effectiveness of soluble steroids compared to particulate.

Cadaver studies indicate that the risk of entering the ascending cervical artery branches at C3-C4 and C4-C5 or the deep cervical artery branches at C5-C6, C6-C7 and C7-T1 was most common if the needle tip was outside the neuroforamen. The number of deep cervical artery branches was highly variable in number and location. Cannulation of the vessel was most common outside the neuroforamen and in the foramen in the inferior–posterior position. A study of 122 prospective cervical transforaminal epidural injections showed the incidence of vascular injection alone was 13.9% and combined epidural and vascular injection 18.9% with no serious complications with needle position adjustment. Other studies show no serious complications in more than 1000 procedures completed. Recommendations include using minimal patient sedation to allow for neurological monitoring, real-time fluoroscopy with nonionic contrast and digital subtraction to maximize detection of vascular uptake, blunt needles, extension tubing to minimize needle movement while changing syringes, a test dose of short acting anesthetic before injection with steroid, and nonparticulate steroids.

Looking at the lumbar spine and the issue of vascular injury, a prospective study shows the incidence of vascular injection of
8.9% and combined injection of 4.2%. There appeared to be a relationship to the level of injection with higher percentages above L5-S1 level. The impact on injection success and complication rate is uncertain. These vascular injections are commonly missed with intermittent fluoroscopy and aspiration of the syringe looking for blood return only has a sensitivity of 44.7%. Neurological insult due to vascular injection during transforaminal epidural injection in the lumbar spine has been seen with injection at the L3-L4 level and above. Similar risks would certainly be present with injection in the thoracic spine. Using similar precautions in the thoracic spine and the upper lumbar spine as are recommended for cervical transforaminal epidural injections would certainly be prudent.

**The Evidence of Selective Lumbar Nerve Root Blocks as a Diagnostic Tool is 2-2, Recommendation Category B**

A systematic review demonstrates that transforaminal epidural steroid injections as a selective block are predictive of success with surgery when associated with surgery at the same level. 46,47

A retrospective study showed that needle electromyography predicted improvement in the Oswestry Disability Index but not pain severity after transforaminal epidural injection. Neither score change would be considered clinically significant. However, the diagnosis was not controlled nor the length of time of symptoms in this study that looked at outcome monthly over 6 months.48

**The Evidence of Epidural Injections as a Short- to Moderate-Term Treatment for Radicular Pain is 2-2, Recommendation Category A**

A randomized controlled trial compared fluoroscopy-guided transforaminal and intralaminar epidural injections in 31 patients with radicular pain of less than 3 months. Their preinjection demographic and pain characteristics were similar. A decrease in pain severity from 7 to 4 in the intralaminar group and 3 in the transforaminal group was significant but comparable statistically. Although both groups sustained a meaningful decrease in pain severity through 6 months, their 1 month scores of 3 versus 1.7 at 1 month and 4.4 versus 2 at 6 months favoring the transforaminal group were significantly different from each other. The weakness of this study is the lack of a fluoroscopy-guided control or a nontreatment control group. The efficacy of transforaminal epidural injections for short to moderate term pain relief is demonstrated.49

The WEST study randomized 228 patients with unilateral sciatica of 1-18 months duration to epidural steroid injection or sham intra-spinal ligament injection. The patients who noted greater than 75% in the Oswestry low back pain disability questionnaire was 12.5% in the treatment and 3.7% in the sham group at 3 weeks with no difference between the groups at 52 weeks. There was no difference between the groups in physical function, return to work rate, or number requiring surgery. However, there was high variability in length of symptoms and diagnosis as well as method of epidural injection. Their conclusion on the lack of efficacy of epidural steroid injections for short term pain relief is weakened by the inherent flaws in their study design.50

A prospective trial of 90 subjects with L5-S1 disc herniation and unilateral leg pain was accomplished with subjects being randomly assigned to receive up to three caudal, translaminar, or transforaminal epidural injections. At the 24 week followup, complete pain relief was seen in 30% of the transforaminal patients, 10% of the intralaminar, and 3% of the caudal. Patients with no pain relief included 43% of the caudal, 40% of the intralaminar, and 17% of the transforaminal. Their hypothesis that the transforaminal patients did better because of medication delivery anteriorly (see Fig. 5) at the site of injury is refuted by a prospective study of 60 patients that showed that intralaminar injection more successfully delivers medication anteriorly in the epidural space (100% versus 75% transforaminal).52 In that study with no control group, the two methods did not significantly differ in the mild improvement in pain from baseline scores at 2 weeks.

A prospective study of 160 patients used serial cervical intralaminar epidural injection every 5 days until greater than 80% pain severity decrease for at least 24 hours compared with continuous bupivacaine with steroids every 4-5 days in patients with radicular pain. All patients sustained their pain reduction for 1 month and 73% for 6 months. The study showed significant difference in benefit only in the group with symptoms greater than 180 days doing better with the continuous injection. There was no control group.53

A randomized trial of caudal epidural injections in 183 patients with back or leg pain of greater than 1 month duration was conducted. The patients received a 20 cc injection with lidocaine only or a 13 cc injection with steroids. There was no statistical difference in the number who noticed no improvement or chose to leave the study for surgical management. However, function as measured by the Oswestry Disability Scale was significantly different between...
groups from 1 to 12 months favoring the steroid treated group. The variation in the symptoms on presentation and the lack of physical evaluation indicates the weakness of their conclusions.

A systematic review noted that the use of epidural steroid injections in radicular lumbosacral pain is limited with a small effect and a time course of effectiveness of less than 3 months. The studies it used noted no change in function, need for surgery, or long term relief. However, this review was based on old studies including epidural injections completed with and without fluoroscopic guidance and with blinded and unblinded study designs. Epidural injections were completed with variable technique and none used the transforaminal approach.

A retrospective study of 20 patients with lumbar radicular pain of 1-18 months duration and failed conservative therapy were treated with epidural steroids. The translaminar and transforaminal treatment groups both improved with the transforaminal group experiencing a statistically better decrease in pain severity. However, even though the groups were matched, the initial pain severity scores were 5.9 for the transforaminal and 7.3 for the translaminar group. Followup was only for 3 weeks. The translaminar group had a shorter duration of improvement and more required surgery.

Few controlled trials for cervical radicular pain have been completed. One study compared cervical intralaminar injections of lidocaine and lidocaine with steroids and noted that 77% of patients had a greater than 50% improvement of pain over 1 year with an average of 3.7 injections per year with no differences between the groups. The patients who did best had the longer benefit from injection.

Two retrospective studies of cervical epidural injections have been completed. In one, intralaminar injections worked better for patients with disc herniation than with stenosis over the 2-week evaluation period. Trends for better outcomes included symptom duration of less than 6 months, younger age, and the presence of cervical radiculopathy. Another looked at the use of cervical transforaminal epidural injections for radicular pain. Of 70 patients studied, 63% were successfully treated with injection while 92% of the 26 that went to surgery had symptom resolution. Patients who went to surgery were younger and had a longer duration of symptoms before injection than those treated successfully with injection. There were no other differences between the groups including the nature of their neurological symptoms.

A systematic review noted some increased benefit with larger volume lumbar epidural injections, postulating that it is related to cadaveric studies showing lysis of adhesions at volumes greater than 30 cc. However, many of the studies were not blinded and symptoms, time course, etiology of symptoms, and type of injection used were too heterogeneous to come to a definitive conclusion.

Early studies have looked at using agents other than corticosteroids for injection. Use of epidural IL-1Ra-enriched autologous conditioned serum showed similar improvement over epidural steroids in a trial of patients with unilateral lower extremity radicular pain over 22 weeks when given weekly injections for 3 weeks. A prospective blinded study of saline versus entanercept, an epidural tumor necrosis factor inhibitor, showed improvement over 6 months with epidural injection for patients with lumbar radicular pain.

The Evidence of Epidural Injections as a Long-term Treatment for Chronic Radicular Pain is 2-2, Recommendation Category B

The use of spinal endoscopic adhesiolysis in 83 patients with chronic refractory low back and extremity pain was compared with endoscopy with injection of corticosteroids and lidocaine. The treatment group had 80% improvement at 2 months, 56% at 6 months and 48% at 1 year, defined as greater than 50% reduction in pain severity score. In the endoscopy group, 33% showed improvement at 1 month and none thereafter. Similarly, a study of adhesiolysis compared with caudal epidural injection showed that 76% achieved a greater than 50% improvement in pain compared to 4% in the caudal epidural group. The pain severity score decrease was from 8 to 4, a clinically meaningful change. Even though Oswestry Disability Index scores also improved, no improvement in employment or meaningful decrease in opiate use was seen in the treatment group over the controls.

The Evidence of Epidural Injections as a Treatment for Low Back Pain is 2-2, Recommendation Category B

A review noted that no type of epidural injection has shown benefit in treatment in chronic low back with and without radicular pain.

A prospective study of 4 cc bilateral transforaminal and 8 cc intralaminar epidural injections for lumbar back pain showed clinically significant decreases in pain for both groups except for patients with lumbar stenosis who did better with transforaminal injection. There was no control group for this study.

The Evidence of Epidural Injections as a Treatment for Radicular Pain for Cervical or Lumbar Stenosis is 2-3, Recommendation Category B

A randomized trial of physical therapy, fluoroscopic-guided intralaminar epidural injection and control subjects was completed in 33 patients with lumbar spinal stenosis. Diagnosis was by history, physical examination, and MRI (anterior-posterior [AP] diameter < 12 mm, lateral diameter < 15 mm). Pain severity decreased in all groups but significantly better over 2 weeks in the injection group. Improvement of pain severity of the control subjects had a very high variance. Physical therapy helped pain severity, mobility, and energy level at various points across 6 months.

Thirty-four patients with lumbar spinal stenosis defined as a decrease in AP canal measurement were treated with a mean of 2.2 caudal epidural injections in a clinical series. Patients with less severe narrowing saw improvements in pain severity (decrease pain severity by 3/10), standing (improved standing tolerance of 2-4 minutes) and walking tolerance (increase by 50 feet), and functional measures. Another clinical series used blind transforaminal epidural injections in patients with computed tomography (CT)-proven lumbar spinal stenosis and noted no parameter predicted
the 34 with good clinical outcome with injection and the 50 who required surgery. A retrospective study of large volume epidural injections for lumbar stenosis showed that patients who received transforaminal injections fared better over 5 weeks than those who received translaminar or caudal epidurals.

A study of cervical intralaminar epidural injections showed better success in treating central stenosis than disc herniation, nerve root compromise, or foraminal stenosis. The study included only 32 subjects with very small subgroups and lots of overlap in symptoms and overlap in pathology on imaging. The drop in pain severity in the successfully treated group of only 1.4 just approaches clinical significance.

**DISCOGENIC PAIN**

The Evidence of Discography as a Diagnostic Tool is 3, Recommendation Category C

The key issue with discography is the issue regarding the gold standard. In many articles, the validity of discography depends on the outcome of surgical fusion, in and of itself a controversial treatment with limited literature support. One study looked at 32 patients with single level discogenic pain by discography and 34 patients with unstable spondylolisthesis and their surgical outcomes. Although their preoperative pain severity scores were comparable, there was a dramatic difference in the number who achieved a pain severity score of less than 2, favoring patients with spondylolisthesis. The authors site these findings as an indication of the poor specificity of discography. However, the efficacy of surgical intervention has not been well studied in controlled trials. And, unless a trial like the one sited takes into account the complex psychosocial factors that influence pain intervention outcome, such trials will be suspect at the least.

A study of asymptomatic patients noted a specificity of 94% and a false-positive rate of 6% when rating a negative discogram as pain severity score < 6/10 at pressures less than 50 psi at a volume less than 3.5 cc. A prospective study of 119 patients with chronic back pain with or without leg pain noted that centralization phenomenon (an ability to eliminate radiating leg pain with spine positioning) was associated with 80-100% specificity but 35-45% sensitivity of concordant pain provocation with discography. Vibration to the spinous process had a sensitivity of 71% and specificity of 63% to concordant pain provocation with discography. Other clinical factors associated with a positive discography included persistent pain between pain attacks, loss of lumbar extension range of motion, and a feeling of vulnerability in the early part of lumbar flexion.

An additional problem is a recent study that correlates future disc degeneration with a history of having a discogram even though previously normal. Disc disease progression was seen in 35% of those with discography compared to 14% without (p < 0.03), including decreased disc space height and signal intensity. In addition, there were 55 new disc herniations in the discography group compared to 22 in the control group (p < 0.0003), with disc herniation preferentially on the side that was injected (p < 0.0006). If these findings are duplicated, it would indicate that in only the direst of situations should discography be pursued less to influence the development of progressive disc degeneration or herniation. Of course, that presumes that strategies could not be developed that lessens this risk.

With these issues in mind, studies of the utility of discography will be discussed. A 4-year prospective controlled longitudinal study of control subjects with or without lumbar discography was completed. Pain on provocative discography did not predict future back pain or back pain disability, work loss, function, or medical treatment. Weak associations were noted with annular fissures on discography and high intensity zones on MRI. Psychometric profiles indicative of distress at the start of the study strongly and independently predicted future back pain (p = 0.01), medication usage (p = 0.002), and work loss (p = 0.01). In summary, in a control population, psychometry better predicted future back pain and its sequelae than did discography.

Fifty-five discs from a control group of 16 healthy volunteers without current back pain (11 men, five women, 32-61 years of age, mean age of 47 years) and 282 discs from a patient group of 90 lumbar back pain patients (59 men, 31 women, 20-70 years of age, mean age of 44.7 years) were recruited to have discography performed using a pressure-controlled manometric technique with an injection rate of 0.05 mL/s and a 3.5 mL restricted total volume. Concordance was rated as familiar pain at greater than or equal 6/10 pain severity level at a pressure less than 50 psi. Only discs with Grade 3 annular tears (Dallas Discogram Scale) were included in the study. Among 55 asymptomatic control group discs, 32 (58.2%) exhibited Grade 3 annular tear. Among 282 patient group discs, 199 (70.6%) exhibited Grade 3 annular tear. Of 199 discs with Grade 3 annular tears, 104 (52.3%) satisfied negative response criteria. Patients showed significantly lower pain tolerance relative to control subjects (p < 0.05). Negative patient discs and asymptomatic subject discs showed similar characteristics. The author’s assertion that pressure-controlled manometric discography using strict criteria may distinguish asymptomatic discs among morphologically abnormal discs with Grade 3 annular tears in patients with suspected chronic discogenic lumbar back pain does not account for the high false-positive rate in the asymptomatic group.

A further prospective study of 107 patients was conducted. Patients received a single physical therapy examination, followed by lumbar provocation discography. Disability and pain intensity ratings were high, and distress was common. Sensitivity, specificity, and positive likelihood ratios for centralization observed during repeated movement testing for pain distribution and intensity changes were 40%, 94%, and 6.9 respectively. In the presence of severe disability, sensitivity, specificity, and positive likelihood ratios were 46%, 80%, 3.2 and for distress, 45%, 89%, 4.1. In the subgroups with moderate, minimal, or no disability, sensitivity and specificity were 37% and 100% and for no or minimal distress 35% and 100%. In summary, pain centralization is not sensitive but is highly specific to positive discography. Specificity is reduced in the presence of severe disability or psychosocial distress.
A prospective study of 47 patients and 94 discs noted that concordant pain was significantly common in the following (p < 0.05):

- Grade 4 or 5 disc degeneration with 88% (30/34) in the concordant pain versus 48% (30/63) in discordant pain and no pain group.
- High intensity zone with 56% (19/34) in the concordant pain versus 30% (19/63) in the discordant or no pain group.
- Combination of the above two findings (53% [18/34] versus 25% [16/63]).
- Fissured and ruptured disc at discogram with 94% (32/34) in the concordant pain versus 57% (36/63) in the discordant or no pain group.
- Contrast beyond inner annulus at CT discogram with 97% (33/34) versus 57% (36/63) in the discordant or no pain group.

Although statistical significance was present, there is high overlap of MRI and CT discography findings, making a clear delineation of a relationship to certain disc defects and MRI or discography abnormalities difficult.80

Studies on cervical discography exist as well. In them, there is noted clear disagreement between MRI and discography results. However, the studies assume that cervical discography is a gold standard, but postoperative studies show using discography results or using clinical impression with concordant MRI changes results in similar postoperative results (which, in and of themselves, are vague at best). Modified Odom’s criteria (excellent = resolution of all preoperative symptoms/pain relieved, good = minimal persistence of preoperative symptoms, fair = relief of some preoperative symptoms, and poor = no change) was used. Discs on T-2 weighted MRI images were identified as white, speckled, and dark as well as flat, bulging, torn and herniated. The percent of negative discography included white 71%, speckled 55%, dark 37%, flat 71%, bulging 65%, torn 41%, and herniated 41%. There were 100/161 discs abnormal on MRI and 79/161 abnormal on discogram in 55 patients. This leaves a 64% correlation of MRI and discography. Twenty-one of 79 positive discograms had a negative MRI. In practical terms, one would not have operated on 42 with abnormal MRI and would have operated on 21 with normal MRI. But again, which is the gold standard? Plus, because no discussion of clinical correlation was noted in their formula, which is the criterion for most surgical treatment programs, it is uncertain which test brings you to the best patient outcome.81,82 The problem is further confounded in the situation where physical examination and MRI do not identify a clear pain generator while discography is grossly abnormal (see Figs. 6 and 7).

The Evidence of Intradiscal Procedures as a Treatment for Discogenic Pain is 2-1, with Strong Studies for the Use of Rami Communicants Blocks for Discogenic Low Back Pain (Category B) and a Recent Study of Intradiscal Laser Coblation for Radicular Discogenic Low Back Pain with Disc Herniation that Needs Corroboration (Category C)

A prospective randomized study compared the therapeutic effect of intradiscal methylprednisolone injection to a saline placebo in 120 patients with discography demonstrated concordant pain. Visual analogue score and Oswestry Disability Index showed no statistical difference in a 12-month study, identifying that intradiscal corticosteroids are not beneficial.83

Figure 6 Patient with normal MRI of lumbosacral spine with concordant pain and complete annular tear on MRI. MRI = magnetic resonance imaging

Figure 7 Patient with cervical degenerative changes on magnetic resonance imaging and a right paracentral disc herniation with dye extravasation into the epidural space seen on discography.
A prospective randomized trial of percutaneous intradiscal radio-frequency thermocoagulation by modifying the duration of heating (using two different time methods) was completed to evaluate the techniques ability to relieve pain and improve functional disability. Sixty patients with chronic low back pain were selected for provocative discography to diagnose discogenic pain and to locate the discs to be treated. From this group, 39 patients were randomly selected and divided into two groups. In the first group, treatment was performed for 120 s and in the second group for 360 s, both at 80°C. There were no statistical differences in pain relief and functional improvement between the two groups (p > 0.05). Pain severity was significantly decreased over 1 month for all patients; for 1 month but not thereafter.84

One study of 100 patients followed prospectively looked at nucleoplasty disc coblation (who received epidural steroids as well) compared to epidural steroids in spinal discogenic pain. Of note, disc space narrowing of greater than 50% was an exclusion in the coblation group but uncertain if so in the epidural group. Pain severity scores were initially recorded as 8.5 with rest and 9.5 with strain. The steroid treated group decreased to 3.2/6.8 comparing rest and strain scores at 3 months and 4.7/7.5 at 8 months. The coblation group decreased to 0.65/2.5 at 3 months and 1.5/3.5 at 8 months, statistically significant at p < .001 and clinically significant decreases for the coblation group at all time points with and without strain.85

Ninety patients with pain severity greater than 5/10 and a single level disc herniation who failed transforaminal epidural steroids were treated with plasma disc decompression with coblation compared to a control group treated with epidural steroids on two occasions. No difference in back pain was seen with the treatment. Initial leg pain severity scores of about 7/10 decreased in the epidural injection group to 5.4 at 6 weeks, 5.0 at 3 months and 5.2 at 6 months. The disc decompression group leg pain severity was 3.5 at 6 weeks, 3 at 3 months and 2.7 at 6 months. These differences are statistically and clinically significant, although the epidural treated group had their pain for 24 months compared to 12 months in the decompression group, leaving some doubt about their findings.86

A study of 49 patients with axial low back pain who failed intradiscal electrothermal annuloplasty were treated at the ramus communicans with half receiving radiofrequency ablation and half receiving lidocaine only. Pain severity scores decreased from 7/10 to 3.8 in the lesion group compared to 7/10 to 6.3 in the sham group at 4 months (p < 0.05).87

Whether using intradiscal electrothermal therapy or discTRODE™, the application of annular radiofrequency electrothermal coagulation does not result in an improvement in pain in patients with discography demonstrated single level discogenic pain. In a placebo controlled trial, 20 patients treated showed a pain severity decrease of 1/10 at 6 months and 1.6 at 12 months compared to 1.4 in the control group. The number of patients reporting a greater than 2-point reduction in pain was equivalent in the two groups at 6 and 12 months.88,89 Brief Pain Inventory and Oswestry scores were not different between groups. This compares with Pauza’s statistically significant pain reduction with intradiscal electrothermal therapy of 2.4 versus 1.2 in the sham group, a difference that does not reach the level of muster for clinically significant reduction in pain in a study where 38% of control patients were responders.90 A case series using the SpineCATH at 65°C for 10 minutes showed a decrease in pain severity from 7.22 to 4.52.91

The use of intrathecal medications is currently at a level 2.3 or 3 only. A number of case series have been completed only with no control group and poor measures of functional and medication use outcome. The percentage of patients with greater than 50% pain improvement ranged from 62-82% although treatment failures approached 25% and the need for reoperation for system failures approached 40%.92 The high initial cost of treatment might be recoverable within 28 months in some studies with better complication rates.

**CONCLUSION**

The following procedures should be considered for their demonstrated utility in the management of spine pain:

- Lumbosacral transforaminal epidural steroids for acute/subacute radicular pain.
- Lumbosacral medial branch and dorsal ramus blocks and radiofrequency ablation for suspected chronic sacral pain.
- Intra-articular SI steroid injections for spondyloarthropathy.
- Rami communicans radiofrequency ablation for lumbosacral discogenic pain.
- Nucleoplasty disc coblation for lumbosacral discogenic radicular pain.
- Spinal cord stimulation of failed back syndrome with persistent radiculopathy.93,94
- The following should be considered for their relative safety in the management of spine pain:
  - SI steroid injection for axial back pain.
  - Lumbar epidural injections for chronic radicular and discogenic pain.
  - Lumbar and cervical medial branch blocks for axial spondylitic pain.

Note: All Diagnostic Tools and Recommendation Categories referred to in the text are from the U.S. Preventive Services Task Force (USPSTF).
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BACKGROUND

Until the latter part of the 1990s, use of longterm opioid therapy for chronic, noncancer pain (CNCP) was essentially prohibited in most states. An early case series study\(^1\) suggested that patients with CNCP, if well chosen, could take opioids long term safely and with fewer severe problems (e.g., abuse/addiction) than previously thought. Pain advocacy groups and groups of pain specialists successfully lobbied state medical boards and legislatures to change statutes and regulations to lift the relative prohibition on opioid use in the CNCP population.\(^2\) In at least 20 states, laws and regulations changed in the late 1990s, dramatically liberalizing use of opioids for CNCP based on model guidelines put forward by groups advocating for much more permissive use of opioids for CNCP.\(^3\) For example, the State of Washington administrative rule 246-919-830 (December 1999), with the force of law, states, “No disciplinary action will be taken against a practitioner based solely on the quantity and/or frequency of opioids prescribed.” Concomitantly, detailed guidelines for physicians related to opioid prescribing for CNCP emerged both at the state and national level. Many of these guidelines focused on commonly agreed-upon best practices such as using a single physician, using a single pharmacy, using opioid treatment agreements to more clearly delineate patient and physician responsibilities, and conducting a comprehensive evaluation for patient risks (e.g., history of substance abuse) at the outset of treatment. There are two key points relevant to this early history: 1) specific guidance on dosing of opioids for CNCP was not offered in any of these statutes, regulations, or guidelines; and 2) the emergence of increasing mortality from accidental poisoning, concomitant with dramatically increasing average daily morphine equivalent doses of the most potent opioids, occurred quickly following the changes to the law.

THE EVIDENCE ON EFFICACY AND EFFECTIVENESS OF OPIOIDS FOR CHRONIC, NONCANCER PAIN

Recent systematic reviews of randomized controlled trials have addressed the efficacy of opioids for CNCP generally,\(^4,5,6\) in older adults,\(^7\) for chronic low back pain,\(^8\) and for neuropathic pain.\(^9\) Although there is evidence for significant pain relief in the short term (average duration of trials: 5 weeks, range: 1-16 weeks), there is no substantial evidence for maintenance of pain relief over longer periods of time, nor significant evidence for improved physical function. In addition, nearly all clinical trials of opioids for CNCP have endured dropout rates on the order of 30%, a fundamental problem which contributes to lowering the level of evidence for most of these studies. Ballantyne\(^5,10\) has expressed the opinion that, with a potentially severe adverse event profile, the failure to maintain analgesic efficacy in the face of escalating doses, particularly in vulnerable patients, could alter the decision to embark on this therapy. Among possible mechanisms for loss of analgesic efficacy, the most likely are development of pharmacologic tolerance and/or opioid-induced hyperalgesia. In addition, the premise that tolerance can be overcome by dose escalation should now be seriously questioned.

Recent observational studies on outcomes of opioids for CNCP suggest nominal effectiveness. In a large cross-sectional Danish survey in 2000,\(^11\) persons with chronic pain on opioids reported...
worse pain relief, functional capacity, and quality of life than persons with chronic pain not using opioids, adjusting for severity. A recent prospective, population-based study on low-back injured workers in Washington State revealed that while morphine equivalent dose (MED) increased significantly over 1 year only a minority of workers reported substantially improved pain and function.

THE MINIMUM CLINICALLY IMPORTANT DIFFERENCE IN OUTCOME

Most randomized trials of efficacy of opioids and other therapies and interventions for CNCP primarily rely on pain relief measured across groups without a specific predetermined degree of pain relief or physical function. Recently, the concept of a minimum clinically important difference (MCID) in pain and function has been used, including patient reported “minimum acceptable” degrees of relief of pain and improvement in function. Unfortunately, for drug approval trials, the Food and Drug Administration (FDA) requires only that pain relief be a primary outcome, and other critical outcomes (improved function or quality of life) are only secondary outcomes. The ideal circumstance would be to preset an MCID for at least pain and function on the order of a 20-30% improvement, and perhaps to use a composite measure including both. Other research gaps related to opioid efficacy and management recently have been identified in a systematic review, including a lack of effectiveness studies on longterm benefits and harms of opioids for CNCP.

THE POOR SAFETY PROFILE OF OPIOIDS—EMERGENCE OF A NATIONAL EPIDEMIC OF MORBIDITY AND MORTALITY

Adverse events most commonly reported in randomized trials include constipation, nausea and vomiting, dizziness, and drowsiness. Much more serious longterm consequences of opioids have been more clearly identified only from observational and epidemiological investigations. These include inhibition of endogenous sex hormone production, hypogonadism, and infertility, immunosuppression, fractures, neonatal abstinence syndrome, sleep disordered breathing, opioid-induced hyperalgesia, nonfatal overdose hospitalizations, and death from unintentional poisoning. Figure 1 demonstrates the dramatic rise in Washington State hospitalizations associated with opioid overdose.

Both Washington (workers’ compensation) and Utah observed a rise in deaths related to unintentional poisoning from prescription opioids beginning within 2 years of state law changes. Similarly, a Drug Enforcement Agency (DEA) national survey of medical examiners conducted in 2001 identified 464 cases of death likely associated with prescription oxycodone; these cases had been validated by examination of stomach contents, which contained prescription opioids and several other drugs commonly prescribed for chronic pain (e.g., antidepressants). Only a minority of these cases had evidence of concomitant alcohol use. More recent studies have clearly documented a national epidemic of unintentional poisoning deaths associated with prescription opioids and a strong linear relationship between mortality and sales of specific prescription opioids (oxycodone, methadone), a surrogate measure of prescription opioid volume and dose. Nationally, by 2005, these deaths exceeded deaths from both firearms and motor vehicle accidents in persons aged 35-54 years. Throughout the period 1999-2006, people aged 35-54 years had higher poisoning death rates involving opioid analgesics as compared with those in other age groups. By 2006, unintentional poisoning deaths accounted for 20% of years of potential life lost before age 65. Thus, preventing these deaths would have a large impact on reducing years of preventable life lost.

The true incidence of physical dependence, pharmacological tolerance, and addiction in this population is unknown; however, it is likely that nearly every patient on opioids chronically, for even a relatively short time, will develop one or more of these forms of dependence. Most problematic is the lack of a rigorous case definition for any of these dependent states, making it challenging for an uninitiated prescribing provider to identify and intervene appropriately.

OPIOID DOSING, TOLERANCE, AND RESPIRATORY DEPRESSION

In the sentinel case series that suggested opioids could be used safely in persons with CNCP the vast majority of patients were taking < 40 mg/day MED. The average dosage range reported in a recent large, population-based observational study was 55 mg/day MED. However, among injured workers in Washington taking long-acting Schedule II opioids, the average daily MED increased substantially between 1996 and 2002, from 80 mg/day MED to 140 mg/day MED. Thus, there is a large “tail” of prescribed dosage. Also, even within the first year following a new low back injury with newly initiated opioids, doses may substantially escalate, and this occurs in the absence of substantial improvement in pain and function. This is the definition of tolerance-doses escalation in the absence of substantial clinical improvement.

A recent study was the first to report a relationship between prescribed opioid dose and overdose events, with a nine-fold increased risk of overdose at doses exceeding 100 mg/day MED compared to...
doses below 20 mg/day MED for CNCP patients. For each fatal overdose in the study, more than seven nonfatal overdoses were observed. It is known that the majority of opioid overdose deaths occur in the home, and only a minority appear to be intentional. Recent observational studies suggest that sleep disordered breathing during non-REM sleep increases with an increased opioid dosage. The potent effect of opioids in depressing central respirations in both animals and humans is well documented. It is also likely that tolerance to analgesic effects of opioids occurs prior to tolerance for respiratory depression. Thus, it is possible that a seemingly normally functioning patient on 200 mg/day MED opioids could die while asleep, particularly if opioids were being used in combination with other central nervous system depressants, which is commonplace.

POLICY RESPONSE TO AN URGENT PUBLIC HEALTH PROBLEM

In response to the epidemic of severe morbidity and mortality, Washington public agencies, in collaboration with academic and practicing pain clinicians, promulgated an opioid dosing guideline in 2007. The core of this guideline is a recommendation for a prescribing provider to seek consultation if a patient reaches 120 mg/day MED and if pain and function have not substantially improved. This yellow flag dosage recommendation has now been included in a new Centers for Disease Control and Prevention issue brief. The Washington Opioid Dosing Guideline has now been updated to include useful tools to allow prescribing providers to conduct best practices when prescribing opioids to patients CNCP with, including 1) a brief tool to track pain and function; 2) tools to screen for past and current substance abuse, alcohol abuse, and significant depression; and 3) prudent advice in conducting targeted urine drug testing.

The Washington legislature passed landmark legislation in March 2010 to address the urgent public health problem, mandating that the boards and commissions representing prescribing providers in Washington repeal all prior rules related to the prescription of opioids for CNCP and create new rules by June 2011. The bill, which received substantial bipartisan support, mandates that the new rules include dosing criteria, guidance on when to seek consultation, and guidance on tracking clinical progress by using assessment tools focusing on pain, physical function, and overall risk for poor outcome.

Through authority granted in 2007, the FDA will implement Risk Evaluation and Mitigation Strategies (REMS) for Schedule II opioids. Potential REMS actions may range from education efforts to more stringent rules including certifying physicians and establishing patient registries. Registries have been mandated for the most recently approved potent opioids. The FDA has stated in public meetings that manufacturers will provide most of the education related to prescribing opioids; but industry-directed efforts to educate physicians have not in themselves substantially changed prescribing practices or reduced morbidity or mortality.

The DEA promulgated new rules, effective June 1, 2010, regarding electronic prescribing of controlled substances, including opioids. The new rules require the same e-prescribing standards for Schedule III-V opioids as for Schedule II opioids and represent a significant step towards defining prescribing standards for electronic medical record systems for controlled substances.

REFERENCES