▼ Review Article

The Role of the Dorsal Root Ganglion in Cervical Radicular Pain: Diagnosis, Pathophysiology, and Rationale for Treatment

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Cervical radicular pain affects 83 per 100,000 adults annually. Diagnosis by means of physical examination, imaging, and electrophysiological studies is characterized by high specificity but low sensitivity. In this review, we focus on the role of the dorsal root ganglion and those treatment modalities that aim at pathophysiological mechanisms occurring after injury to the dorsal root ganglion. Cervical nerve injury initiates multiple events that lead to changes in nerve function and result in spontaneous firing at the dorsal root ganglion. Among these, inflammation and changes in ion-channel function play a pivotal role. Although many treatment modalities are described in the literature, the available evidence for efficacy does not allow us to formulate definitive conclusions on the optimal therapy. A lack of evidence is reported for cervical spine surgery. Interlaminar epidural steroid administration and radiofrequency techniques adjacent to the cervical dorsal root ganglion have the highest, but still weak recommendations. *Reg Anesth Pain Med 2006;31:152-167.*

Key Words: Dorsal root ganglion, Cervical radicular pain, Radiculopathy, Pathophysiology, Treatment, Evidence.

Cervical radicular pain is pain perceived in the upper limb, is shooting or electric in quality, and is caused by irritation and/or injury of a cervical spinal nerve.[1,2] This condition was first described in the literature by Parkinson in 1817, as a "rheumatic disease of the deltoid muscle."[3] Almost 1 century later, Dejerine (1914) formulated the concept of "cervical radiculitis."[4] In the classification of the International Association for the Study of Pain (1994), cervical radicular pain is defined as pain perceived as arising in the upper limb caused by ectopic activation of nociceptive afferent fibers in a spinal nerve or its roots or other neuropathic mechanisms.[5] This is a problematic definition, as the presence of ectopic activation has rarely, if ever, been shown in the clinical setting. Cervical radicular pain should be distinguished from cervical radiculopathy, a condition in which an objective loss of sensory and/or motor function is present. Radicular pain and radiculopathy are therefore not synonymous, although they are frequently not differentiated in the literature. The former is a symptom caused by ectopic impulse generation. The latter also includes neurologic signs. The 2 conditions may nonetheless coexist and may be caused by the same clinical entities (e.g., narrowing of the intervertebral foramen; intervertebral disc herniation; and radiculitis caused by arteritis, infection, or inflammatory exudates).[5] The 2 syndromes can be part of a continuum, and radiculopathy may follow radicular pain as the underlying disease progresses.

A variety of treatment modalities for cervical radicular pain are described, but the optimal treatment approach remains unclear.[1] In clinical practice, treatment is often started conservatively,[6] but an interventional or surgical treatment may be considered as part of a multidisciplinary approach in the management of intractable pain. The apprecia-

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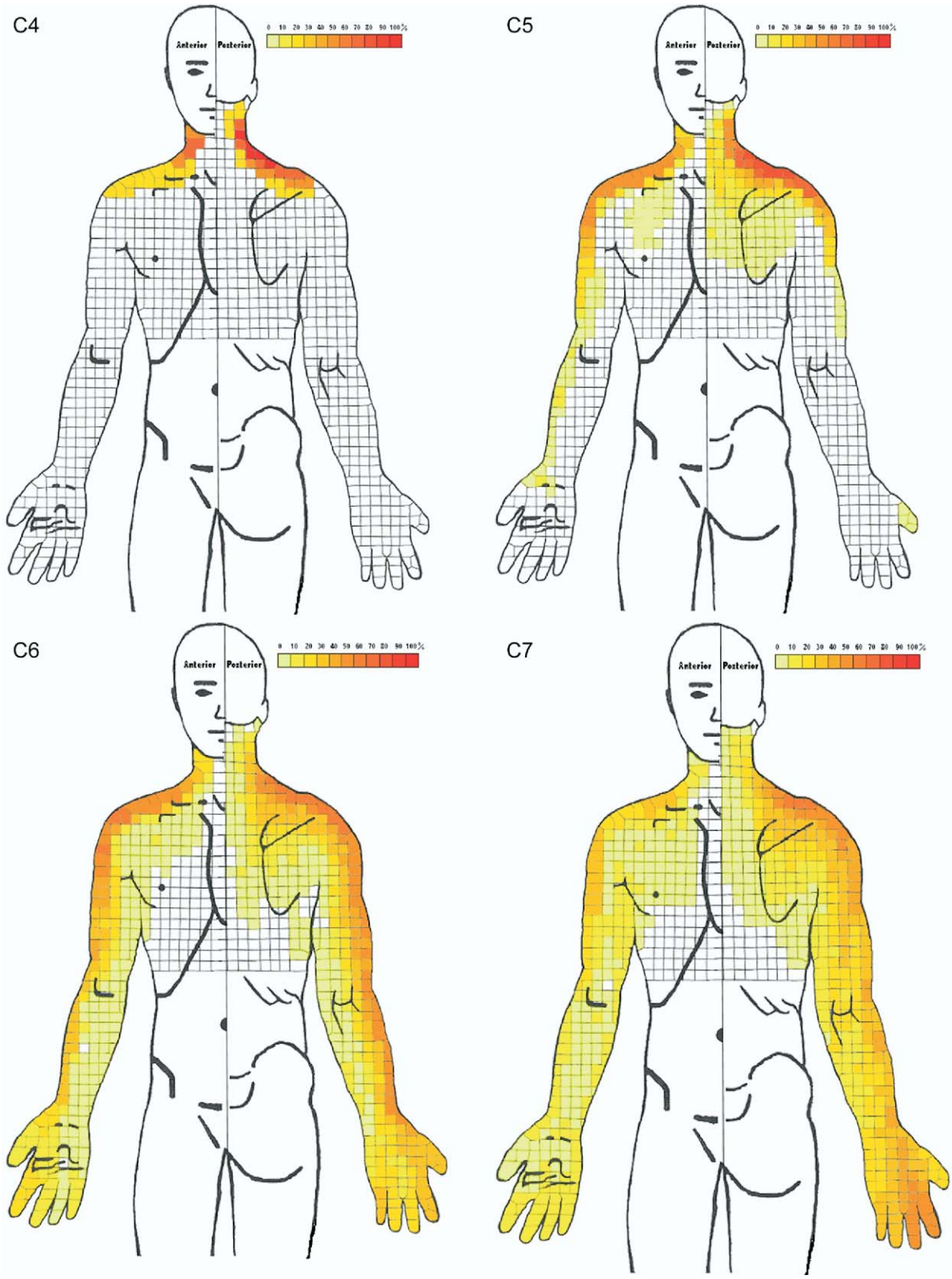

Fig 1. Percent occurrence of symptom provocation per bit for the C4 to C7 roots. (Reprinted with permission.[9])

tion of the potential effect of the different treatment possibilities can only be made based on a good understanding of the pathophysiology.

The aim of this review is to describe the clinical picture and diagnosis of cervical radicular pain. We will focus in particular on the role of the dorsal root ganglion (DRG) and those treatment modalities that aim at the underlying pathophysiological mechanisms occurring after nerve injury in the DRG. Central sensitization and changes in the dorsal horn will not be discussed.

Clinical Picture and Epidemiology

In cervical radicular pain, the symptoms and signs are related to dysfunction of cervical spinal nerve roots and should be perceived along the distribution of the affected nerve root.[2,7,8] This distribution was verified in clinical experiments in which radicular pain was elicited in the characteristic distributions by mechanical stimulation of cervical spinal nerves with a needle under fluoroscopic control. The distribution of the different patterns of the cervical nerves is documented by Slipman et al.[9] and shown in Figure 1. Bogduk[2] summarized the distributions as follows: pain from C4 is restricted to the neck and suprascapular regions. Pain from C5 extends into the upper arm, whereas pain from C6 and C7 extends from the neck and shoulder into the forearm and hand. In both instances, the pain covers the lateral border of the upper limb but that of C7 extends more onto the dorsal aspect. Pain from successive spinal nerves overlaps considerably, and no particular region of the upper limb is characteristic of any particular segment.[2] Somatic-referred pain from the zygapophyseal joint or from the cervical intervertebral disc can have distributions similar to radicular pain when the pain is perceived in the proximal upper limb.[10,11] However, when pain is distributed in the forearm and or hand, it is far more likely to be radicular in origin. Nevertheless, radicular pain should not be restricted to a dermatome and might be perceived in any of the structures innervated by the affected nerve because cervical spinal nerves are also distributed to deep structures, such as muscles, joints, and ligaments as well as skin.[2]

In the literature, the natural history of cervical radicular pain or radiculopathy is not described in detail, and data on incidence and prevalence are scarce. The most frequently used epidemiological data are from Rochester, MN (1976-1990). In this study, the incidence was calculated based on the information from the computerized medical record-linkage system from the Mayo Clinic and its 2 affiliated hospitals. The authors claim that their database is essentially an enumeration of the population of Rochester. They calculated in a population between 13 and 91 years an annual incidence of cervical radiculopathy of 83 per 100,000.[12] Although the authors classified the patients as suffering from radiculopathy, we believe that the patient population they describe also included cervical radicular pain because sensory changes were only reported in 33% and weakness in 64%. The average annual age-adjusted incidence rates per 100,000 people were 107 for males and 64 for females. The highest incidence was found in the age group 50 to 54 years with an average of 203 per 100,000 people. In 15% of the patients, a history of physical exertion or trauma preceded the onset of symptoms, and 41% of the patients had a previous history of lumbar radiculopathy. According to this study, the most frequently involved level was C7 in 45% to 60% of the cases. Level C6 represents approximately 20% to 25% and levels C5 and C8 each represent approximately 10% of the cases.[12] However, other distributions were reported, with C5 being the most frequently treated level.[13] Considering the limited information available, a high-quality population-based epidemiologic study on incidence and natural history of cervical radicular pain appears warranted.

Diagnosis

As with other types of spinal pain, if cervical radicular pain does not resolve spontaneously within 3 months, confirmation should be sought to rule out vertebral column infections and cancer (e.g., Pancoast tumor) before further symptomatic treatment is offered. Somatic referred pain and shoulder pathology should also be excluded because their clinical presentation may be similar to

Table 1. Diagnostic Test for Cervical Radicular Pain

Test	Description
Spurlings test	Spine extended with head rotated to affected shoulder while axially loaded. Reproduction of the patient's shoulder or arm pain indicates possible cervical nerve root compressions.[16]
Shoulder abduction test	The patient lifts a hand above his or her head. A positive result is the decrease or disappearance of the radicular symptom.[18]
Axial manual traction test	In supine position an axial traction force corresponding to 10 to 15 kg is applied. A positive finding is the decrease or disappearance of the radicular symptom.[18]

radicular pain.[2,14] Neurologic examination of patients with cervical radicular pain includes testing of strength, muscle stretch reflexes, and sensation.[15] The following clinical tests have been reported as useful for the diagnosis of cervical radicular pain: the neck compression test or Spurling test,[16] shoulder abduction test,[17] and axial manual traction test.[18] These tests are described in Table 1. The validity of 3 tests (Spurling, axial manual traction, and shoulder abduction test) in the diagnosis of root compression in cervical disc disease was investigated regarding radicular pain, neurologic signs, and root compression signs in myelography. All tests had a high specificity (81%-100%) but a low sensitivity (26%-50%) for the validity parameters.[18] Spurling's test has also been validated in a controlled trial by using electromyography as a reference with comparable results (sensitivity of 30% and specificity of 93%).[19] Despite low sensitivity, the 3 investigated tests are considered valuable aids in the clinical diagnosis of a patient with neck and arm pain.[18]

The most commonly used complementary diagnostic tools to establish the etiology of cervical radicular pain are imaging techniques and electrophysiological studies. Imaging studies provide information relative to anatomic abnormalities, whereas electrophysiological studies allow detection of neurologic dysfunction. The primary role of plain radiography is to diagnose injuries of the cervical spine.[20,21] Computed tomography scanning is particularly useful for cortical bony structures. It is more sensitive to changes in bone than is magnetic resonance imaging (MRI) but has limited ability to detect soft-tissue lesions.[22-24] Magnetic resonance imaging is better suited to identify changes of the disc, spinal cord, nerve root, and surrounding soft-tissue structures.[23] Some authors state that MRI is the imaging modality of choice in patients with cervical radicular pain, and this appears to be consistent with current practice.[20,23] However, data on specificity and sensitivity of various imaging techniques in this setting are limited because a diagnostic gold standard for cervical radicular pain does not exist. Moreover, prospective studies showed abnormal MRI scans of the cervical spine in 19% to 28% of asymptomatic subjects, depending on their age.[25,26] Therefore, interpretation of any imaging finding must be done in the context of a patient's clinical presentation.[25,27]

Electromyography is used to sample motor unit behavior in selected limb muscles as well as the cervical paravertebral muscles to detect neurophysiological pathology related to a cervical nerve root or roots. Nerve conduction studies are also performed in conjunction with electromyography to rule out other causes of symptoms such as a peripheral nerve involvement.[28] Several other electrophysiological procedures, such as analysis of motor unit action potentials and the evaluation of evoked potential latencies, have been suggested to increase the sensitivity,[29] but until now electromyography remains the most sensitive method.[30,31] An initial report on the use of quantitative sensory testing as a selection tool for appropriate treatment for patients suffering lumbar radiculopathy caused by disc herniation indicates potential value, but there are no results on cervical radicular pain available yet.[32] Diagnostic procedures such as imaging techniques, electrophysiological testing, and quantitative sensory testing provide useful complementary data, but they cannot replace clinical diagnosis.

Radiologic imaging provides excellent morphological detail of the pathology and its relation to the neuraxis and so allows exclusion of other processes such as cancer,[33] infection,[34] and neurovascular pathology.[35] However, in patients with chronic radicular pain, it is often not possible to determine with any certainty which disc and/or nerve root is symptomatic in the degenerative cervical spine.[36] Before deciding on any interventional treatment option, attempts should be made to confirm that the level as determined by clinical examination and ancillary investigations is truly the one that causes the signs and symptoms. Therefore, selective diagnostic nerve root blocks may be recommended. This technique, injecting a small volume (0.5-1 mL) of local anesthetic adjacent to the DRG, controlled by prior injection of nonionic contrast medium under direct real-time fluoroscopy, has been described by van Kleef et al.[37]

Wolff et al.[38] studied the accuracy of selective diagnostic nerve root blocks in the lumbar region by using standard dermatomal maps. They found that interpretation of an adequately performed segmental nerve block in the presumed dermatome is more reliable when the overlap of neighboring dermatomes is taken into account. In an extensive review on the value of neural blockade for diagnostic and prognostic purposes, no data were obtained on cervical spinal nerve blocks.[39] The authors conclude that the confusion and complexity that typifies diagnosis in chronic spinal pain may justify selective use of diagnostic blocks that make anatomic and physiologic sense, even if their validity is incompletely proved.[39]

In conclusion, diagnosis of cervical radicular pain and radiculopathy requires a complete medical history, clinical diagnosis using standardized test methods of physical examination, imaging techniques, electrophysiological investigation, and determination of the symptomatic level by means of diagnostic selective nerve root blocks. Nevertheless,

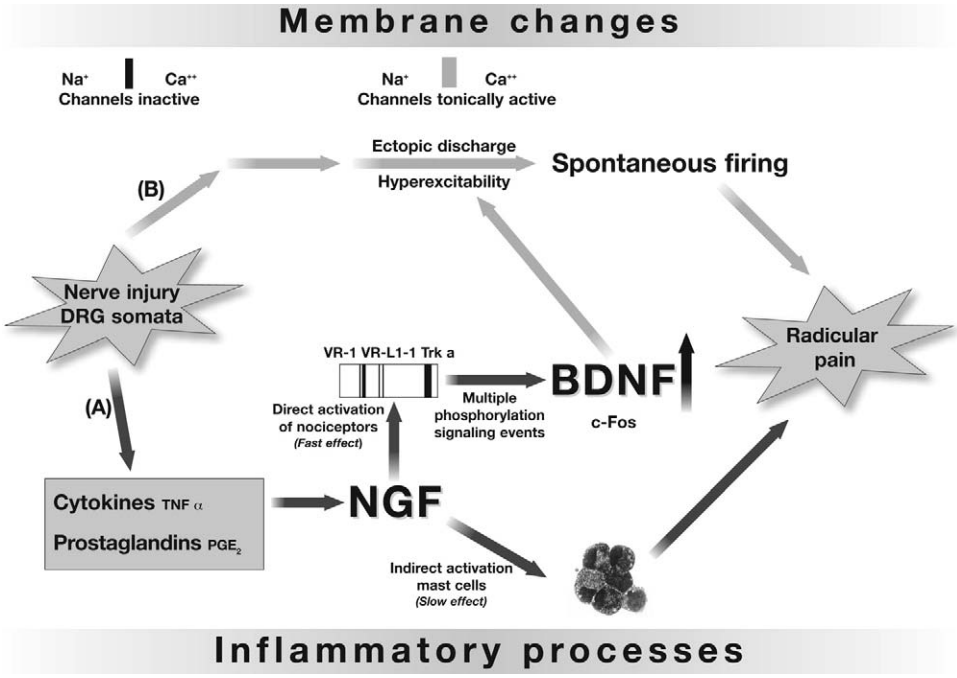

Fig 2. Known changes at the dorsal root ganglion after nerve injury at the dorsal root ganglion somata include an inflammatory cascade (A) with release of inflammatory cytokines and prostaglandins ultimately leading to the release of nerve growth factor (NGF). NGF has a simultaneous effect via direct activation of nociceptors "fast-effect" binding to the MAPK-kinase receptor tyrosine-kinase-A (TrkA) or vanilloid receptors (VR1) and heat-sensitive vanilloid like receptors (VR-L1). These results in multiple signaling events, which then cause massive release of brain-derived neurotrophic factor (BDNF) and increased c-Fos expression. In addition, NGF initiates an indirect activation "slow effect" via mast cells and degranulation product release; the latter results in a further release of NGF. In parallel, there are changes in the ion channels (B) whereby Na+ and Ca2+ channels become tonically active. As a result of ion channel modification ectopic discharge, hyperexcitability and spontaneous firing occurs at the DRG. This spontaneous firing together with the increased BDNF expression is the primary mechanism underlying radicular pain.

the discrepancy found in clinical practice between symptoms and pathology identified with imaging techniques and electrophysiological testing often remains striking. Moreover, recent research on genetically determined differences in sensitivity to pain highlight the problem of interindividual variability, which is often observed in clinical practice in which pain symptoms and treatment effects vary among patients with similar clinical conditions.[40,41]

Pathophysiology

Despite the fact that the exact pathophysiological mechanisms underlying radicular pain in humans are not yet fully understood, fundamental research in various animal models has provided important insights. In line with the literature on the pathophysiology of lumbar radicular pain, 2 major mechanisms in the nerve are thought to induce cervical radicular pain: (1) nucleus pulposus material leaking onto the nerve root and/or (2) compression of the nerve root by anatomic abnormalities. Either of these pathogenic mechanisms will induce 2 processes in the nerve: (1) an inflammatory reaction, and, related to this, (2) changes in ion-channel functioning. Eventually, these effects cause a pattern of hyperexcitability and spontaneous ectopic activity in the DRG, which is interpreted as pain. In addition, discharges enter the spinal cord and induce central sensitization at the synapses located in the dorsal horn.[42] Howe et al.[43] in a classic paper in 1977 recognized that repetitive spontaneous firing took place after minimal compression of the normal DRG. It was this article that provided the stimulus for further research into the pathophysiological changes in the DRG as a driving mechanism for pain after an injury to a nerve.[44,45] In this section, we will discuss nerve and DRG inflammation and changes in ion-channel functioning as possible causes of cervical radicular pain[43] (Fig 2).

Inflammatory Process

Inflammation of a cervical DRG and/or nerve root can be caused by injury or exposure to nucleus pulposus material of the cervical disc, leading to the

release of many trophic molecules and cytokines that play a role in the development of pain.[46] Among these molecules, prostaglandins (PGs) and nerve growth factor (NGF) are the most important.

Arachidonic acid, the most abundant precursor of PG in mammals, is released from cell membrane phospholipids by the action of phospholipase present in nucleus pulposus material.[47] PGs are generated from arachidonic acid by the enzyme cyclo-oxygenase (COX), of which there are 2 isoforms.[48] COX-1 is a constitutive enzyme present in platelets, stomach, intestines, and kidneys. In these tissues, it performs a "housekeeping" function to synthesize PGs that regulate normal-cell activities. COX-2 is the form induced at inflammatory sites in various cell types (i.e., macrophages, synoviocytes, fibroblasts, and so on). Although it has been shown that COX-2 is induced in dorsal root neurons after peripheral injury in rats,[49] its role in DRG and/or nerve root injury remains unproven. Several findings, however, suggest that it may play a causative role in the development of radicular pain. COX-2 mediates central PG synthesis, which may be important in the generation of pain.[50] Basal release of PGs occurs in the spinal cord and dorsal root ganglia. Acute and chronic inflammation increases the expression of COX-2 and the release of PGE2 and PGI2.[47] Inflammatory cytokines (e.g., tumor necrosis factor-α [TNF-α]) and interleukins are involved in the initiation of intracellular changes through activation of different mitogen-activated protein kinase (MAPK) pathways.[51] In a rat model of experimental disc herniation, an increased expression of TNF-α in the DRG was described.[52]

Nerve growth factor is released after injury at the DRG somata and acts via both a fast and a slow effect.[53-55] The fast effect of NGF is an activity on nociceptors such as vanilloid receptors and heat-sensitive receptors such as vanilloid-like receptors. Vanilloid receptors are present in tyrosine kinase A–positive C-fibers; no expression is observed in cells with myelinated axons.[56] Slow effects of NGF include the upregulation of various molecules, including c-Fos, within the neuron. A_β and A_δ-fibers are involved in the NGF-mediated slow effect but C-fibers are not.[57] After nerve injury at the DRG, only some fibers may be directly damaged; however, a degree of modulation takes place in all neurons.[58] Nerve injury exposes noninjured afferents to an inflammatory environment that affects their function and activity. Signals generated during Wallerian degeneration may affect neighboring intact afferents. Nerve growth factor, for example, regulates the expression of neuropeptide genes in adult sensory neurons.[59] NGF expression in the DRG has previously been linked to increased expression of brain-derived neurotrophic factor (BDNF).[60-63] Recently, Obata et al.[64] described extracellular signal-regulated protein kinase signaling in the DRG after injury in the DRG somata as a link between NGF and BDNF expression and proposed this as a mechanism for radicular pain. There is also evidence that the increase in BDNF, which is constitutively expressed in sensory neurons and transported from DRG to terminals in the spinal cord,[65] may be a major inducer of the central mechanisms of inflammatory-induced hyperalgesia.[66-68]

In summary, although few studies have addressed this issue directly, indirect data suggest that inflammation may well be a major mechanism in the pathophysiology of cervical radicular pain, mainly as a result of injury or exposure of nervous tissue to nucleus pulposus material. This induces a cascade of events. Importantly, after nerve injury, both injured and noninjured fibers are involved in this inflammatory process in which NGF and BDNF are key players.

Ion-Channel Modulation

Nerve injury initiates membrane changes whereby the functioning of voltage-gated Na, K, and Ca ion channels is modified. Although neurophysiologic doctrine has traditionally referred to the voltage-gated Na channel, it is now clear that there are at least 9 genes that encode molecularly and physiologically distinct Na channels. Plasticity in Na channel gene expression is accompanied by electrophysiological changes that prime these cells to fire spontaneously or at inappropriately high frequencies.[69] Many workers have identified increased expression of voltage-dependent Na channels in the DRG after injury.[70,71] Cummins et al.[72] recognized Na_v 1.3 channels as responsible for abnormal hyperexcitability of DRG neurons. Furthermore, Na_v 1.9 channels and possibly also Na_v 1.3 channels are dramatically reduced both in radicular pain and in neuropathic pain.[73] The result is a shift in resting membrane potential, which could relieve resting inactivation. This implies that neurons both injured and noninjured are primed and in a hyperexcitable state and can fire repetitively, leading to cervical radicular pain.

The reduction of K currents in DRG cells has been illustrated after peripheral nerve axotomy.[74] Potassium channels play an important role in the generation of ectopic discharges and the reduction in K currents after peripheral injury contributes to neuronal excitability.[75] However, the exact function of K currents in ectopic discharge generation mechanisms is not yet clear. To further elucidate the role of Na, Ca, and K ion channels, Liu et al.[76] examined

the effect of Na, Ca, and K ion channel blockers in a model of neuropathic pain (spinal nerve ligation 7-14 days prior). It was shown that ectopic discharges from DRG were inhibited in the presence of Na channel blockers, suggesting that Na channels are critical for the ability of damaged nerves to generate repetitive firing of action potentials. Nonspecific Ca channel blockers (Cd^{+}, Co^{2+}, Ni^{2+}) also were effective in reducing the rate of ectopic discharges when applied to the DRG,[76] as were a specific L-type blocker (verapamil) and N-type blocker (omega-conotoxin). Blockade with omega-conotoxin is an irreversible blockade producing long-lasting inhibition of ectopic discharges.[77,78]

In addition to dysregulated channel expression, altered channel trafficking also might play a role in the pathophysiological process after nerve injury. For correct physiological functioning, ion transport proteins must be targeted to the appropriate domains of cell membranes as shown in several fundamental studies.[79,80] In conclusion, after nerve injury, Na ion channels are primarily involved in hyperexcitability of the neuron fibers, whereas Na, K, and Ca ion channels are focal points in the generation of ectopic neuronal discharge.

Spontaneously Firing DRG

As indicated previously, it has been difficult to pinpoint the causative dysfunction in the DRG that is responsible for radicular pain. Part of the reason for this difficulty is that effects at various molecular targets are tightly interlinked. A modulation of the ion channels in the membrane of the DRG neurons has been reported. There is concurrent increased expression of BDNF, which has recently been shown to directly and rapidly gate Na channels. This BDNF-induced gating of ion channels causes membrane depolarization of neurons and eventually results in the firing of action potentials.[81,82] Finally, both pathways can result in repetitive spontaneous firing after a transient nerve injury. It has been shown that many ion channels may be modulated in a nerve injury. The real crux of the pathophysiology is to elucidate which modulated ion channels have functional significance in causing pain.[45,74,83] The application of new techniques such as gene arrays, a methodological approach to analyze gene expression (messenger RNA) profiles in neuropathological conditions, and proteomic technologies used to determine the genome sequences and the interpretation of the corresponding proteins that are encoded therein, may help to speed up the process of identifying a more complete list of proteins that are components in a pathophysiological process of ongoing radicular pain.

Rationale and Level of Evidence for Treatment Modalities Targeting the Cervical DRG and/or Nerve Root

Chronic cervical radicular pain is a complex syndrome that has a high impact on patients' quality of life.[84] An integrated approach involving psychological counseling, physical therapy, cognitive behavioral treatment, and symptomatic management of the pain is recommended.[85] The multidisciplinary evaluation also aims at providing guidance for the selection of any treatment.[20,86] In a later section, we limit our discussion to treatment modalities, which, at least in theory, have a mode of action that interferes with the pathophysiological mechanisms described earlier at the level of cervical DRG or nerve root.

Methods

Literature was identified by a search in electronic databases, including Cochrane Controlled Trials Register (Issue 2, 2005), OLDMEDLINE from 1960 to 1966, MEDLINE from 1966, and EMBASE from 1974 to December 2004. We conducted literature searches specifically for the treatment of cervical radicular pain using for MEDLINE the exploded Mesh headings "radiculopathy" combined with the key word "cervical" and another combining the Mesh headings "pain," "neck," and "radiculopathy or spinal nerve roots"; additionally, a search using the abstract words "radicular," "pain," and "cervical" was conducted. For EMBASE, we used the following EMTREES: "radicular pain," "neck," "chronic pain," "cervical neuralgia," and "therapy" and limited the search to "human." Combining the results of those searches with "drug" and/or "pharmacological therapy" yielded no references. The publications were screened based on the abstract. The reference lists from identified articles and relevant textbooks were manually searched for additional papers. Pharmaceutical companies were contacted to obtain unpublished information or data presented at congresses or in nonindexed journals.

Application of the level of evidence and the grade of recommendation was done by an experienced epidemiologist (MP) (methodological quality of the evidence) and 2 clinicians (MVK and JVZ) (clarity of the risk/benefit balance) according to the authoritative and recently published evidence-based guidelines by Guyatt for the American College of Chest Physicians.[87] This proposed grading provides information on the clarity of the risk/benefit balance and about the methodological quality of the evidence resulting in strength of recommendation from strong to very weak as shown in Table 2. We looked for the publications with the highest level of

Table 2. Grade of Recommendations According to The American College of Chest Physicians

Grade of Recommendation	Clarity of Risk/Benefit	Methodological Strength of Supporting Evidence	Implications
1A	Clear	RCTs without important limitations	Strong recommendation can apply to most patients in most circumstances without reservation
1C+	Clear	No RCTs but strong RCT results can be unequivocally extrapolated, or overwhelming evidence from observational studies	Strong recommendation; can apply to most patients in most circumstances
1B	Clear	RCTs with important limitations (inconsistent results, methodological flaws)	Strong recommendations; likely to apply to most patients
1C	Clear	Observational studies	Intermediate-strength recommendation; may change when stronger evidence is available
2A	Unclear	RCTs without important limitations	Intermediate-strength recommendation; best action may differ depending on circumstances or patients' or societal values
2C+	Unclear	No RCTs but strong RCT results can be unequivocally extrapolated, or overwhelming evidence from observational studies	Weak recommendation; best action may differ depending on circumstances or patients' or societal values
2B	Unclear	RCTs with important limitations (inconsistent results, methodological flaws)	Weak recommendation; alternative approaches likely to be better for some patients under some circumstances
2C	Unclear	Observational studies	Very weak recommendations; other alternatives may be equally reasonable

NOTE. Method used for evaluating the methodological strength of the available evidence and the clarity of the risk/benefit balance reprinted with permission of the American College of Chest Physicians.[86]
Abbreviation: RCT, randomized clinical trial.

evidence for the different treatment modalities of cervical radicular pain targeting the cervical DRG and/or nerve root; the summary is listed in Table 3.

Therapies Targeting the Inflammatory Changes (NGF and BDNF Modulation)

Pharmacological anti-inflammatory treatment relies mainly on the use of nonsteroidal anti-inflammatory (NSAIDs) drugs, corticosteroids, and perhaps in the future TNF-α inhibitors.

NSAIDs

NSAIDs, the most commonly used analgesics, are potent agents for the treatment of inflammatory pain. Their analgesic action (inhibiting PG synthesis) is postulated to be primarily at peripheral sites of inflammation,[88] but evidence is accumulating that PGs are also produced in the DRG and the spinal cord.[47,89] NSAIDs inhibit PG synthesis through inhibition of COX enzymes, which is responsible for both therapeutic and unwanted effects. Unfortunately, serious cardiovascular adverse events have been described recently after long-term use of selective COX-2 inhibitors.[90-92] Nonsteroidal anti-inflammatory drugs are efficacious in a variety of pain syndromes,[93,94] but none of the different NSAIDs have been investigated in the management of cervical radicular pain. Hence, no evidence is available to support or refute efficacy in this setting.

Corticosteroids

The anti-inflammatory effect of corticosteroids is achieved by the inhibition of the phospholipase A2–initiated arachidonic acid cascade.[95] Also, a local anesthetic-like effect is postulated.[96] The epidural administration of corticosteroids, either by the interlaminar or transforaminal route, aims at delivering the medication in the surroundings of the inflamed nerve root. We did not find published studies comparing intralaminar versus transforaminal approaches. A clinical trial comparing intramuscular steroid with cervical epidural steroid administration indicates good pain relief in 68% of the patients receiving epidural steroid 1 year after the last injection compared with 11.8% of the patients treated intramuscularly (level 2B recommendation).[97] The Cochrane review indicates limited evidence for effectiveness of interlaminar epidural injection of steroids for cervical radicular pain.[98] In a retrospective cohort study on the complications of fluoroscopic-guided interlaminar cervical epidural injections, only minor complications were mentioned (in 17% of the patients). These complica-

Table 3. Evidence for Treatment of Cervical Radicular Pain

Treatment	Publication	Type	Study Characteristics	Clarity of Risk/Benefit Balance	Level of Evidence	Results
Interlaminar steroid	(Stav A, et al, 1993)[98]	Prospective, randomized, epidural (n = 25) vs intramuscular (n = 17)	Blinded evaluator concealment	Unclear : 2	B	Good pain relief in 68% of epidural group vs 12% in intramuscular group
Transforaminal steroid (fluoroscopy guided)	(Vallee JN, et al, 2001)[105]	Non-comparative prospective (n = 32)	2 evaluators Well-defined endpoints	Unclear : 2	C	53% success rate at 6 months
Transforaminal steroid (CT guided)	(Cyteval C, et al, 2004)[106]	Non-comparative prospective (n = 30)	Evaluator not blinded Well-defined endpoints	Unclear : 2	C	60% success rate at 6 months
RF cervical DRG	(van Kleef M, et al, 1996)[38]	Prospective, randomized, double-blind RF (n = 9) vs sham (n = 11)	Independent evaluator Concealment of allocation	Unclear : 2	B	Significant more pain reduction in RF group vs sham at 8 weeks
RF cervical DRG	(Slappendel R, et al, 1997)[132]	Prospective, randomized, double-blind RF 40°C (n = 29) vs RF 67°C (n = 32)	Independent evaluator Concealment of allocation	Unclear : 2	B	Significant pain reduction equal in both groups at 3 months
Pulsed RF cervical DRG	(Van Zundert J, et al, 2003)[137]	Non-comparative prospective (n = 18)	Independent evaluator Well-defined endpoints	Unclear : 2	C	72% success rate at 8 weeks and 33% at 1 year
Neck surgery	(Persson L, et al, 1997)[139]	Prospective, randomized, surgery (n = 27) vs physiotherapy (n = 27) or cervical collar (n = 27)	Evaluator not involved in study but not blinded Allocation concealment	Unclear : 2	B	Surgery not more effective as cervical collar or physiotherapy after 3 and 12 months

NOTE. Publications with the highest level of evidence for the specific management of cervical radicular pain.
Abbreviations: CT, computed tomography; RF, radiofrequency; DRG, dorsal root ganglion.

tions resolved without morbidity.[99] However, case reports mention nerve injury or spinal cord damage after cervical epidural steroid injections.[100,101] Intrinsic spinal cord damage was reported in 2 patients receiving intravenous sedation, which is now generally considered as contraindicated.[100] The transforaminal route has gained in popularity over the last decade because it is supposed to deliver the drug as close as possible to the inflammatory nerve root.[1,102,103] Vallee et al.[104] performed a prospective noncomparative study using fluoroscopy as control for the needle placement. After 6 months, 53% of the patients experienced excellent or good pain relief (level C evidence). Also, good pain relief was reported in 60% of the patients after computed tomography–guided cervical periradicular foraminal steroid infiltrations in an open prospective study with 6 months follow-up (level C evidence).[105] Recently, several case reports indicate the possibility of serious adverse events such as spinal cord injury after cervical transforaminal injections, which are hypothesized to be related to intra-arterial injection of particulate steroid occluding critical vessels that supply the spinal cord.[106-109] Hence, some doubt the suitability of this approach[110] and even suggest to temporarily abandon the technique above the L3 level until more scientific data are available.[111]

At this moment, the debate regarding efficacy and safety of cervical transforaminal versus interlaminar injection of corticosteroids is ongoing. Therefore, both techniques should be handled with caution and only after the patient has been fully informed of the risks. Based on the unclear risk/benefit balance, the use of transforaminal epidural steroids yields a very weak (2C) recommendation.

TNF-α Inhibitors

Basic research shows that TNF-α is involved in the development of nucleus pulposus-induced nerve injuries,[112] and TNF-α inhibitors can provide pain relief. This is in accordance with recent findings indicating that TNF-α inhibitors attenuate the elevated BDNF levels induced by nucleus pulposus application to the nerve root.[112] Open-label trials using systemically injected TNF-α inhibitors in the management of lumbar radicular pain indicate a potential benefit of this treatment option.[113-116]

There, are, however, no data on the treatment of cervical radicular pain.

Therapies Targeting Ion Channel Modulation

Sodium Channel Blockers

Sodium channel blockers such as the anticonvulsant drugs carbamazepine and oxcarbazepine have been widely used for the treatment of central and peripheral neurogenic pain.[117] Valproic acid is used also for the treatment of neuropathic pain, although a randomized clinical trial indicated that valproic acid is not superior to placebo for the management of polyneuropathy.[118] Mexiletine has been reported to be effective in a variety of neuropathic pain syndromes. More recent reports, however, question the efficacy of oral mexiletine in neuropathic pain, making it difficult to draw definitive conclusions.[119-121]

Calcium Channel Antagonists

Modulation of calcium channels may have an additional role to play in the management of cervical radicular pain. Gabapentin is known to bind to the $\alpha_2\delta$ unit of voltage-gated–dependent calcium channels.[122] Several randomized, large-scale studies are now available.[123] The efficacy of gabapentin was shown in patients with postherpetic neuralgia and painful diabetic neuropathy in 2 placebo-controlled trials.[124,125] A report of 10 cancer patients with neuropathic pain in head or neck shows pain relief with gabapentin.[126] Recently, Sabatowski et al.[127] have shown that pregabalin, another drug modulating the calcium channels, is also effective in treating neuropathic pain.

In conclusion, ion channel antagonists are commonly used as coanalgesics for the treatment of neuropathic pain,[128] but their value has never been investigated in the management of cervical radicular pain. It should be stressed that for most of the pharmacological agents a more complex mode of action is described, working via several ion channels.

Other Treatments Targeting the Cervical DRG and/or Nerve Root

Radiofrequency/Pulsed Radiofrequency

Radiofrequency (RF) treatment has been used in a variety of pain syndromes because of its ability to interrupt the pain conducting pathways.[85,129,130] However, the mode of action is not yet clear. The efficacy of RF treatment adjacent to the cervical DRG has been shown in 2 randomized clinical trials.[37,131] Van Kleef et al.[37] showed a significant reduction in pain 8 weeks after RF at 67°C compared with sham treatment (level B evidence). Additionally, Slappendel et al.[131] found that treatment with RF at 40°C was equally effective as treatment at 67°C (level B evidence). According to 2 systematic reviews, there is currently limited evidence that radiofrequency treatment of the dorsal root ganglion is more effective than placebo in chronic cervical radicular pain.[130,132]

Recently, pulsed radiofrequency (PRF) was introduced in clinical practice as a non- or minimally neurodestructive modification of conventional RF heat lesions.[133] A potential mechanism of action of radiofrequency/PRF treatment may be via an NGF-initiated intracellular pathway with downstream modification of intracellular signaling. Higuchi et al.[134] showed that PRF treatment adjacent to the DRG induced c-Fos expression (as an indicator of neuronal activation) in the dorsal horn 3 hours after the intervention. Furthermore, 7 days after RF and PRF treatment adjacent to the rat cervical DRG, c-Fos is expressed in pain-modulating zones of the dorsal horn.[135] A first clinical audit[136] on the use of PRF treatment adjacent to the cervical DRG of patients suffering chronic pain in the cervical region radiating into the arm or the head showed a positive outcome in 72% of the patients after 8 weeks and in 33% after 1 year (level C evidence). No side effects or neurologic complications were reported. The available literature on RF and PRF adjacent to the cervical DRG yields a weak (2B) recommendation for RF and a very weak (2C) recommendation for PRF. Considering the potential better risk/benefit balance of PRF, further research is justified.

Neck Surgery

Cervical spondylosis and/or disc herniation can cause cervical radicular pain by compressing the roots or the spinal cord. Surgical techniques for decompression with or without anterior interbody fusion are often performed to reduce the pain and disability but are associated with a small but definite risk.[137] A randomized clinical trial from Person et al.[138] in patients with long-lasting cervical radicular pain indicates that 3 different treatment modalities, (cervical collar, physiotherapy, or surgery) appear to be equally effective in the long term, and a multidisciplinary rehabilitation with cognitive behavioral therapy is recommended, indicating a level B evidence that surgery is not more effective than conservative therapy in the long term.[138] These data are summarized in a systematic review of Cochrane group from Fouyas et al. who concluded that it is not clear whether the short-term risks of surgery are offset by any long-term benefits.[137] In 2004, another systematic review by

Jacobs et al.[139] appeared in the Cochrane database, aiming at evaluating different anterior interbody fusion techniques for cervical degenerative disc disease. Although this review was not specific for cervical radicular pain or radiculopathy, some of the referred studies were dealing with it. This review could not formulate definitive conclusions regarding the different cervical anterior body fusion techniques because of the low quality of the trials.

Based on the available evidence of efficacy and the risk/benefit ratio, there is weak (2B) recommendation against the use of neck surgery for cervical radicular pain. Furthermore, after an additional analysis of the patients from Persson's randomized clinical trial on pain, coping, emotional state, and physical function, a multidisciplinary treatment with cognitive behavioral therapy and psychological interventions was recommended.[140]

Potential Future Treatment Modalities

MAPK Pathways

Future therapies in the management of cervical radicular pain originating at the DRG may include drugs such as mast cell stabilizers, which could potentially abate some of the effects of NGF. Because the p38 MAPK pathway is involved in multiple normal physiological processes, inhibiting the pathway as anti-inflammatory therapy might not be best achieved by inhibiting p38 MAPK itself, but rather by targeting upstream or downstream signal transduction.[141] Specific downstream targets of p38 MAPK could include tyrosine kinase inhibitors such as an inhibitor of extra signal–regulated protein kinase signaling protein.

Vanilloid Receptors

Other emergent therapies include vanilloid receptor blockers; a trial of resinferatoxin (a ultrapotent capsaicin analog) has been used in the management of patients with hypersensitive disorders of the lower urinary tract.[142]

Long-acting Local Anesthetics

Local anesthetics act through inhibition of the Na channels and play a major role in the identification of the causative nerve structure. The duration of action is, however, relatively short, which makes these drugs not suited for the management of chronic pain syndromes. Recent reports of animal experiments with long-acting local anesthetics such as butamben suspension, which was administered epidurally to rats with nerve injury-induced allodynia indicate that multiple doses were required for several days to provide prolonged analgesia.[143] Tonicaine was injected intrathecally in rats. The product produced sensory blockade of duration significantly longer than that elicited by bupivacaine. It has, however, a narrow therapeutic index, with substantial neurotoxicity in rats, which may limit its clinical value.[144] Those reports indicate that this type of molecule may be an alternative treatment option. This must be confirmed in human subjects.

Tricyclic Antidepressants

The mode of action of these compounds is classically attributed to serotonin and norepinephrine reuptake blockade.[145,146] It was suggested that amitryptiline may also be a potent blocker of neuronal sodium channels,[147] and recent literature shows the possible role of tricyclic antidepressants as long-acting local anesthetics.[148-150] Preliminary studies of amitryptiline showed no better nerve blockade properties than current local anesthetic and risks for neurotoxicity have to be considered.[151]

Gene Therapy

Gene therapy has made advances where a number of specific disease entities are now being treated, including severe combined immunodeficiency in children. Vectors constructed from recombinant herpes simplex virus have special utility for gene transfer to the nervous system. Subcutaneous inoculation of the herpes simplex virus vectors can be used to transduce neurons of the dorsal root ganglion to provide a therapeutic effect in models of polyneuropathy and chronic regional pain. In human trials, direct injection of replication-competent herpes simplex virus into brain tumors has proven safe, and herpes simplex virus gene transfer by subcutaneous inoculation for the treatment of chronic intractable pain is the next trial about to commence.[152]

Conclusions

Chronic cervical radicular pain and radiculopathy affects approximately 1 in 1,000 adults, with a high impact on the patient's quality of life. These patients require a multidisciplinary approach and are therefore frequently referred to pain centers. The most frequently recognized etiology is root injury by disc herniation and stenosis of the intervertebral foramen. Pathophysiological changes in the DRG after nerve injury are hypothesized to play an important role in cervical radicular pain. We focus in this review in particular on currently available and emerging treatment modalities that aim at pathophysiological changes occurring after nerve injury at the cervical DRG. This nerve injury induces inflammatory processes and membrane changes leading to spontaneously firing DRG. The inflammatory process that is

initiated by the release of many trophic molecules and cytokines results in the release of NGF, which acts via a "fast effect" and a "slow effect." The fast effect is obtained via direct activation of nociceptors leading to the expression of BDNF by multiple phosphorylation signaling events. The slow effect or indirect activation occurs via mast cells and degranulation product release. Nerve injury also initiates membrane changes whereby sodium and calcium channels become overly active. As a result of ion channel modification, there is ectopic discharge, hyperexcitability, and spontaneous firing DRG, which may cause radicular pain.

The available pharmacological therapies interfering with the previously described pathophysiological mechanisms such as NSAIDs, TNF-α inhibitors, and the different ion channel antagonists have documented efficacy for the management of a variety of pain syndromes, although controlled trials evaluating their efficacy for the treatment of cervical radicular pain are largely lacking.

Interventional treatments targeting the cervical DRG and/or nerve root have been studied in more detail. Although spine surgery for relieving cervical radicular pain is often performed, there is lack of evidence to support its effectiveness. The less invasive percutaneous interventional pain management techniques are somewhat better documented, although direct comparisons between techniques such as intralaminar and transforaminal epidural steroid administration are lacking. Further research in this area is necessary to enable more definitive conclusions. In addition, newer therapies currently under development might offer alternative treatment options in the future.

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References

1. Rathmell JP, Aprill C, Bogduk N. Cervical transforaminal injection of steroids. *Anesthesiology* 2004; 100:1595-1600.
2. Bogduk N. *Medical Management of Acute Cervical Radicular Pain: An Evidence-Based Approach*. 1st ed. Newcastle, Australia: The Newcastle Bone and Joint Institute; 1999.
3. Parkinson J. *An Essay on the Shaking Palsy*. London: Paternoster Row; 1817.
4. Dejerine J. *Sémiologie des Affections du Système Nerveux*. Paris: Masson et cie; 1914.
5. Merskey H, Bogduk N. *Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms*. 2nd ed. Seattle, WA: IASP Press; 1994.
6. Saal JS, Saal JA, Yurth EF. Nonoperative management of herniated cervical intervertebral disc with radiculopathy. *Spine* 1996;21:1877-1883.
7. Devereaux MW. Neck and low back pain. *Med Clin North Am* 2003;87:643-662.
8. Bland J. Cervical spine syndromes. *J Muscoloskel Med* 1986;3:23-41.
9. Slipman CW, Plastaras CT, Palmitier RA, Huston CW, Sterenfeld EB. Symptom provocation of fluoroscopically guided cervical nerve root stimulation. Are dynatomal maps identical to dermatomal maps? *Spine* 1998;23:2235-2242.
10. Dwyer A, Aprill CA, Bogduk N. Cervical zygapophysial joint pain patterns. I/ A study in normal volunteers. *Spine* 1990;15:453-457.
11. Schellhas KP, Smith M, Grundy C, Pollei S. Cervical discogenic pain. Prospective correlation of magnetic resonance imaging and discography in asymptomatic subjects and pain sufferers. *Spine* 1996;21:300-311.
12. Radhakrishnan K, Litchy WJ, O'Fallon WM, ? LT. Epidemiology of cervical radiculopathy. A population-based study from Rochester, Minnesota, 1976 through 1990. *Brain* 1994;117:325-335.
13. Sluijter ME. Cervicobrachialgia. In: Sluijter ME, ed. *Radiofrequency, Part 2*. Meggen, Switzerland: Flivopress, SA; 2003:9-22.
14. Date E, Gray L. Electrodiagnostic evidence for cervical radiculopathy and suprascapular neuropathy in shoulder pain. *Electromyogr Clin Neurophysiol* 1996; 36:333-339.
15. Fager CA. Identification and management of radiculopathy. *Neurosurg Clin N Am* 1993;4:1-12.
16. Spurling R, Scoville W. Lateral rupture of the cervical intervertebral discs: A common cause of shoulder and arm pain. *Surg Gynecol Obstet* 1944;78:350-358.
17. Davidson RI, Dunn EJ, Metzmaker JN. The shoulder abduction test in the diagnosis of radicular pain in cervical extradural compressive monoradiculopathies. *Spine* 1981;6:441-446.
18. Viikari-Juntura E, Porras M, Laasonen EM. Validity of clinical tests in the diagnosis of root compression in cervical disc disease. *Spine* 1989;14:253-257.
19. Tong HC, Haig AJ, Yamakawa K. The Spurling test and cervical radiculopathy. *Spine* 2002;27:156-159.
20. Wainner RS, Gill H. Diagnosis and nonoperative management of cervical radiculopathy. *J Orthop Sports Phys Ther* 2000;30:728-744.
21. Nguyen GK, Clark R. Adequacy of plain radiography in the diagnosis of cervical spine injuries. *Emerg Radiol* 2005;11:158-161.

22. Brown BM, Schwartz RH, Frank E, Blank NK. Preoperative evaluation of cervical radiculopathy and myelopathy by surface-coil MR imaging. *AJR Am J Roentgenol* 1988;151:1205-1212.
23. Jahnke RW, Hart BL. Cervical stenosis, spondylosis, and herniated disc disease. *Radiol Clin North Am* 1991;29:777-791.
24. Modic MT, Masaryk TJ, Mulopulos GP, et al. Cervical radiculopathy: Prospective evaluation with surface coil MR imaging, CT with metrizamide, and metrizamide myelography. *Radiology* 1986;161:753-759.
25. Boden SD, McCowin PR, Davis DO, et al. Abnormal magnetic-resonance scans of the cervical spine in asymptomatic subjects. A prospective investigation. *J Bone Joint Surg Am* 1990;72:1178-1184.
26. Teresi LM, Lufkin RB, Reicher MA, et al. Asymptomatic degenerative disk disease and spondylosis of the cervical spine: MR imaging. *Radiology* 1987;164:83-88.
27. Healy JF, Healy BB, Wong WH, Olson EM. Cervical and lumbar MRI in asymptomatic older male lifelong athletes: Frequency of degenerative findings. *J Comput Assist Tomogr* 1996;20:107-112.
28. Dimitru D. *Electrodiagnostic Medicine*. Philadelphia, PA: Hanley & Belfus, Inc; 1995.
29. Haldeman S. The electrodiagnostic evaluation of nerve root function. *Spine* 1984;9:42-48.
30. Eisen A. The utility of proximal nerve conduction in radiculopathies: The cons. *Electroencephalogr Clin Neurophysiol* 1991;78:171-172; discussion 67.
31. Partanen J, Partanen K, Oikarinen H, et al. Preoperative electroneuromyography and myelography in cervical root compression. *Electromyogr Clin Neurophysiol* 1991;31:21-26.
32. Schiff E, Eisenberg E. Can quantitative sensory testing predict the outcome of epidural steroid injections in sciatica? A preliminary study. *Anesth Analg* 2003;97:828-832.
33. Clar SA, Cianca JC. Intracranial tumor masquerading as cervical radiculopathy: A case study. *Arch Phys Med Rehabil* 1998;79:1301-1302.
34. Friedmand DP, Hills JR. Cervical epidural spinal infection: MR imaging characteristics. *AJR Am J Roentgenol* 1994;163:699-704.
35. Hetzel A, Berger W, Schumacher M, Lucking CH. Dissection of the vertebral artery with cervical nerve root lesions. *J Neurol* 1996;243:121-125.
36. Anderberg L, Annertz M, Brandt L, Saveland H. Selective diagnostic cervical nerve root block—Correlation with clinical symptoms and MRI-pathology. *Acta Neurochir (Wien)* 2004;146:559-565; discussion 565.
37. van Kleef M, Liem L, Lousberg R, et al. Radiofrequency lesion adjacent to the dorsal root ganglion for cervicobrachial pain: A prospective double blind randomized study. *Neurosurgery* 1996;38:1127-1131; discussion 31-32.
38. Wolff AP, Groen GJ, Crul BJ. Diagnostic lumbosacral segmental nerve blocks with local anesthetics: A prospective double-blind study on the variability and interpretation of segmental effects. *Reg Anesth Pain Med* 2001;26:147-155.
39. Hogan QH, Abram SE. Neural blockade for diagnosis and prognosis. A review. *Anesthesiology* 1997;86:216-241.
40. Mogil JS. The genetic mediation of individual differences in sensitivity to pain and its inhibition. *Proc Natl Acad Sci U S A* 1999;96:7744-7751.
41. Mogil JS, Wilson SG, Bon K, et al. Heritability of nociception II. "Types" of nociception revealed by genetic correlation analysis. *Pain* 1999;80:83-93.
42. Guo W, Zou S, Guan Y, et al. Tyrosine phosphorylation of the NR2B subunit of the NMDA receptor in the spinal cord during the development and maintenance of inflammatory hyperalgesia. *J Neurosci* 2002;22:6208-6217.
43. Howe JF, Loeser JD, Calvin WH. Mechanosensitivity of dorsal root ganglia and chronically injured axons: A physiological basis for the radicular pain of nerve root compression. *Pain* 1977;3:25-41.
44. Wall PD, Devor M. Sensory afferent impulses originate from dorsal root ganglia as well as from the periphery in normal and nerve injured rats. *Pain* 1983;17:321-339.
45. Devor M, Saltzer Z. Pathophysiology of damaged nerves in relation to chronic pain. In: Wall PD MR, ed. *Textbook of Pain*. London: Churchill Livingstone; 1999:129-164.
46. Kang JD, Georgescu HI, McIntyre-Larkin L, et al. Herniated cervical intervertebral discs spontaneously produce matrix metalloproteinases, nitric oxide, interleukin-6, and prostaglandin E2. *Spine* 1995; 20:2373-2378.
47. Vanegas H, Schaible HG. Prostaglandins and cyclooxygenases [correction of cycloxygenases] in the spinal cord. *Prog Neurobiol* 2001;64:327-363.
48. Herschman HR. Prostaglandin synthase 2. *Biochim Biophys Acta* 1996;1299:125-140.
49. Ebersberger A, Grubb BD, Willingale HL, et al. The intraspinal release of prostaglandin E2 in a model of acute arthritis is accompanied by an up-regulation of cyclo-oxygenase-2 in the spinal cord. *Neuroscience* 1999;93:775-781.
50. McCrory C, Fitzgerald D. Spinal prostaglandin formation and pain perception following thoracotomy: A role for cyclooxygenase-2. *Chest* 2004;125:1321-1327.
51. Woolf CJ, Allchorne A, Safieh-Garabedian B, Poole S. Cytokines, nerve growth factor and inflammatory hyperalgesia: The contribution of tumour necrosis factor alpha. *Br J Pharmacol* 1997;121:417-424.
52. Murata Y, Onda A, Rydevik B, et al. Distribution and appearance of tumor necrosis factor-alpha in the dorsal root ganglion exposed to experimental disc herniation in rats. *Spine* 2004;29:2235-2241.
53. Andreev N, Dimitrieva N, Koltzenburg M, McMahon SB. Peripheral administration of nerve growth factor in the adult rat produces a thermal hyperalgesia that requires the presence of sympathetic postganglionic neurones. *Pain* 1995;63:109-115.
54. Bennett G, al-Rashed S, Hoult JR, Brain SD. Nerve growth factor induced hyperalgesia in the rat hind paw is dependent on circulating neutrophils. *Pain* 1998;77:315-322.

55. Shu X, Mendell LM. Nerve growth factor acutely sensitizes the response of adult rat sensory neurons to capsaicin. *Neurosci Lett* 1999;274:159-162.
56. Tominaga M, Caterina MJ, Malmberg AB, et al. The cloned capsaicin receptor integrates multiple pain-producing stimuli. *Neuron* 1998;21:531-543.
57. Chung JM, Chung K. Importance of hyperexcitability of DRG neurons in neuropathic pain. *Pain Practice* 2002;2:87-97.
58. Obata K, Yamanaka H, Fukuoka T, et al. Contribution of injured and uninjured dorsal root ganglion neurons to pain behavior and the changes in gene expression following chronic constriction injury of the sciatic nerve in rats. *Pain* 2003;101:65-77.
59. Lindsay RM, Harmar AJ. Nerve growth factor regulates expression of neuropeptide genes in adult sensory neurons. *Nature* 1989;337:362-364.
60. Apfel SC, Wright DE, Wiideman AM, et al. Nerve growth factor regulates the expression of brain-derived neurotrophic factor mRNA in the peripheral nervous system. *Mol Cell Neurosci* 1996;7:134-142.
61. Michael GJ, Averill S, Nitkunan A, et al. Nerve growth factor treatment increases brain-derived neurotrophic factor selectively in TrkA-expressing dorsal root ganglion cells and in their central terminations within the spinal cord. *J Neurosci* 1997;17: 8476-8490.
62. Thompson SW, Bennett DL, Kerr BJ, et al. Brain-derived neurotrophic factor is an endogenous modulator of nociceptive responses in the spinal cord. *Proc Natl Acad Sci U S A* 1999;96:7714-7718.
63. Lever I, Cunningham J, Grist J, et al. Release of BDNF and GABA in the dorsal horn of neuropathic rats. *Eur J Neurosci* 2003;18:1169-1174.
64. Obata K, Yamanaka H, Dai Y, et al. Activation of extracellular signal-regulated protein kinase in the dorsal root ganglion following inflammation near the nerve cell body. *Neuroscience* 2004;126:1011-1021.
65. Zhou XF, Rush RA. Endogenous brain-derived neurotrophic factor is anterogradely transported in primary sensory neurons. *Neuroscience* 1996;74:945-953.
66. Cho HJ, Kim JK, Zhou XF, Rush RA. Increased brain-derived neurotrophic factor immunoreactivity in rat dorsal root ganglia and spinal cord following peripheral inflammation. *Brain Res* 1997;764:269-272.
67. Groth R, Aanonsen L. Spinal brain-derived neurotrophic factor (BDNF) produces hyperalgesia in normal mice while antisense directed against either BDNF or trkB, prevent inflammation-induced hyperalgesia. *Pain* 2002;100:171-181.
68. Kerr BJ, Bradbury EJ, Bennett DL, et al. Brain-derived neurotrophic factor modulates nociceptive sensory inputs and NMDA-evoked responses in the rat spinal cord. *J Neurosci* 1999;19:5138-5148.
69. Waxman SG. Acquired channelopathies in nerve injury and MS. *Neurology* 2001;56:1621-1627.
70. Matzner O, Devor M. Hyperexcitability at sites of nerve injury depends on voltage-sensitive Na+ channels. *J Neurophysiol* 1994;72:349-359.
71. Zhang JM, Donnelly DF, Song XJ, Lamotte RH. Axotomy increases the excitability of dorsal root ganglion cells with unmyelinated axons. *J Neurophysiol* 1997; 78:2790-2794.
72. Cummins TR, Aglieco F, Renganathan M, et al. Nav1.3 sodium channels: Rapid repriming and slow closed-state inactivation display quantitative differences after expression in a mammalian cell line and in spinal sensory neurons. *J Neurosci* 2001;21:5952-5961.
73. Abe M, Kurihara T, Han W, et al. Changes in expression of voltage-dependent ion channel subunits in dorsal root ganglia of rats with radicular injury and pain. *Spine* 2002;27:1517-1524; discussion 1525.
74. Everill B, Kocsis JD. Reduction in potassium currents in identified cutaneous afferent dorsal root ganglion neurons after axotomy. *J Neurophysiol* 1999;82:700-708.
75. Devor M. Potassium channels moderate ectopic excitability of nerve-end neuromas in rats. *Neurosci Lett* 1983;40:181-186.
76. Liu X, Zhou JL, Chung K, Chung JM. Ion channels associated with the ectopic discharges generated after segmental spinal nerve injury in the rat. *Brain Res* 2001;900:119-127.
77. Boland LM, Morrill JA, Bean BP. Omega-conotoxin block of N-type calcium channels in frog and rat sympathetic neurons. *J Neurosci* 1994;14:5011-5027.
78. Churchill D, Macvicar BA. Biophysical and pharmacological characterization of voltage-dependent Ca2+ channels in neurons isolated from rat nucleus accumbens. *J Neurophysiol* 1998;79:635-647.
79. Chou KC. Insights from modeling three-dimensional structures of the human potassium and sodium channels. *J Proteome Res* 2004;3:856-861.
80. Muth TR, Caplan MJ. Transport protein trafficking in polarized cells. *Annu Rev Cell Dev Biol* 2003;19:333-366.
81. Rose CR, Blum R, Kafitz KW, et al. From modulator to mediator rapid effects of BDNF on ion channels. *Bioessays* 2004;26:1185-1195.
82. Kafitz KW, Rose CR, Thoenen H, Konnerth A. Neurotrophin-evoked rapid excitation through TrkB receptors. *Nature* 1999;401:918-921.
83. Amir R, Michaelis M, Devor M. Membrane potential oscillations in dorsal root ganglion neurons: Role in normal electrogenesis and neuropathic pain. *J Neurosci* 1999;19:8589-8596.
84. Daffner SD, Hilibrand AS, Hanscom BS, et al. Impact of neck and arm pain on overall health status. *Spine* 2003;28:2030-2035.
85. Van Zundert J, Raj P, Erdine S, van Kleef M. Application of radiofrequency treatment in practical pain management: State of the art. *Pain Practice* 2002;2: 269-278.
86. Kerns RD, Habib S. A critical review of the pain readiness to change model. *J Pain* 2004;5:357-367.
87. Guyatt G, Schunemann HJ, Cook D, et al. Applying the grades of recommendation for antithrombotic and thrombolytic therapy: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;126:179S-187S.

88. Vinegar R, Truax JF, Selph JL. Quantitative comparison of the analgesic and anti-inflammatory activities of aspirin, phenacetin and acetaminophen in rodents. *Eur J Pharmacol* 1976;37:23-30.
89. Baba H, Kohno T, Moore KA, Woolf CJ. Direct activation of rat spinal dorsal horn neurons by prostaglandin E2. *J Neurosci* 2001;21:1750-1756.
90. Topol E, Falk G. A coxib a day won't keep the doctor away. *Lancet* 2004;364:639-640.
91. Ray WA, Stein CM, Daugherty JR, et al. COX-2 selective non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease. *Lancet* 2002; 360:1071-1073.
92. Mamdani M, Juurlink D, Lee D, et al. Cyclo-oxygenase-2 inhibitors versus non-selective non-steroidal anti-inflammatory drugs and congestive heart failure outcomes in elderly patients: A population-based cohort study. *Lancet* 2004;363:1751-1756.
93. Hawkey CJ. COX-2 inhibitors. *Lancet* 1999;353:307-314.
94. van Tulder MW, Scholten RJ, Koes BW, Deyo RA. Nonsteroidal anti-inflammatory drugs for low back pain: A systematic review within the framework of the Cochrane Collaboration Back Review Group. *Spine* 2000;25:2501-2513.
95. Crocker IC, Zhou CY, Bewtra AK, et al. Glucocorticosteroids inhibit leukotriene production. *Ann Allergy Asthma Immunol* 1997;78:497-505.
96. Johansson A, Hao J, Sjolund B. Local corticosteroid application blocks transmission in normal nociceptive C-fibres. *Acta Anaesthesiol Scand* 1990;34:335-338.
97. Stav A, Ovadia L, Sternberg A, et al. Cervical epidural steroid injection for cervicobrachialgia. *Acta Anaesthesiol Scand* 1993;37:562-566.
98. Peloso P, Gross A, Haines T, et al. Medicinal and injection therapies for mechanical neck disorders. *Cochrane Database Syst Rev* 2005:CD000319.
99. Botwin K, Castellanos R, Rao S, et al. Complications of fluoroscopically guided interlaminar cervical epidural injections. *Arch Phys Med Rehabil* 2003;84:627-633.
100. Hodges SD, Castleberg L, Miller T, et al. Cervical epidural steroid injection with intrinsic spinal cord damage. *Spine* 1998;23:2137-2141.
101. Field J, Rathmell JP, Stephenson JH, Katz NP. Neuropathic pain following cervical epidural steroid injection. *Anesthesiology* 2000;93:885-888.
102. Rowlingson JC. *Epidural Steroids: Do They Have a Place in Pain Management?* Barcelona: V. Permanyer Publications, 1996.
103. Hession WG, Stanczak JD, Davis KW, Choi JJ. Epidural steroid injections. *Semin Roentgenol* 2004; 39:7-23.
104. Vallee JN, Feydy A, Carlier RY, et al. Chronic cervical radiculopathy: Lateral-approach periradicular corticosteroid injection. *Radiology* 2001;218:886-892.
105. Cyteval C, Thomas E, Decoux E, et al. Cervical radiculopathy: Open study on percutaneous periradicular foraminal steroid infiltration performed under CT control in 30 patients. *AJNR Am J Neuroradiol* 2004;25:441-445.
106. Baker R, Dreyfuss P, Mercer S, Bogduk N. Cervical transforaminal injection of corticosteroids into a radicular artery: A possible mechanism for spinal cord injury. *Pain* 2003;103:211-215.
107. Brouwers PJ, Kottink EJ, Simon MA, Prevo RL. A cervical anterior spinal artery syndrome after diagnostic blockade of the right C6-nerve root. *Pain* 2001;91:397-399.
108. Rosenkranz M, Grzyska U, Niesen W, et al. Anterior spinal artery syndrome following periradicular cervical nerve root therapy. *J Neurol* 2004;251:229-231.
109. Karasek M, Bogduk N. Temporary neurologic deficit after cervical transforaminal injection of local anesthetic. *Pain Med* 2004;5:202-205.
110. Rathmell JP, Benzon HT. Transforaminal injection of steroids: Should we continue? *Reg Anesth Pain Med* 2004;29:397-399.
111. Huntoon MA, Martin DP. Reply to Drs. Raghavendra and Harney. *Reg Anesth Pain Med* 2005;30:208-209.
112. Onda A, Murata Y, Rydevik B, et al. Infliximab attenuates immunoreactivity of brain-derived neurotrophic factor in a rat model of herniated nucleus pulposus. *Spine* 2004;29:1857-1861.
113. Korhonen T, Karppinen J, Malmivaara A, et al. Efficacy of infliximab for disc herniation-induced sciatica: One-year follow-up. *Spine* 2004;29:2115-2119.
114. Karppinen J, Korhonen T, Malmivaara A, et al. Tumor necrosis factor-alpha monoclonal antibody, infliximab, used to manage severe sciatica. *Spine* 2003;28:750-753.
115. Shin K. Treatment of neck and back pain originating from herniated nucleus pulposus with tumor necrosis factor alpha inhibitor. In: *International Society for the Study of the Lumbar Spine*. Porto, Portugal: SpineWeek vzw; 2004.
116. Genevay S, Guerne PA, Gabay C. [Efficacy of tumor necrosis factor-alpha blockade for severe sciatica?]. *Rev Med Suisse Romande* 2004;124:543-545.
117. McQuay H, Carroll D, Jadad AR, et al. Anticonvulsant drugs for management of pain: A systematic review. *BMJ* 1995;311:1047-1052.
118. Otto M, Bach FW, Jensen TS, Sindrup SH. Valproic acid has no effect on pain in polyneuropathy: A randomized, controlled trial. *Neurology* 2004;62:285-288.
119. Nishiyama K, Sakuta M. Mexiletine for painful alcoholic neuropathy. *Intern Med* 1995;34:577-579.
120. Wright JM, Oki JC, Graves L 3rd. Mexiletine in the symptomatic treatment of diabetic peripheral neuropathy. *Ann Pharmacother* 1997;31:29-34.
121. Wallace MS, Magnuson S, Ridgeway B. Efficacy of oral mexiletine for neuropathic pain with allodynia: A double-blind, placebo-controlled, crossover study. *Reg Anesth Pain Med* 2000;25:459-467.
122. Gee NS, Brown JP, Dissanayake VU, et al. The novel anticonvulsant drug, gabapentin (Neurontin), binds to the alpha2delta subunit of a calcium channel. *J Biol Chem* 1996;271:5768-5776.
123. Hansson PT, Dickenson AH. Pharmacological treatment of peripheral neuropathic pain conditions

based on shared commonalities despite multiple etiologies. *Pain* 2005;113:251-254.
124. Backonja M, Beydoun A, Edwards KR, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: A randomized controlled trial. *JAMA* 1998;280:1831-1836.
125. Rowbotham M, Harden N, Stacey B, et al. Gabapentin for the treatment of postherpetic neuralgia: A randomized controlled trial. *JAMA* 1998;280:1837-1842.
126. Sist TC, Filadora VA 2nd, Miner M, Lema M. Experience with gabapentin for neuropathic pain in the head and neck: Report of ten cases. *Reg Anesth* 1997; 22:473-478.
127. Sabatowski R, Galvez R, Cherry DA, et al. Pregabalin reduces pain and improves sleep and mood disturbances in patients with post-herpetic neuralgia: Results of a randomised, placebo-controlled clinical trial. *Pain* 2004;109:26-35.
128. Sindrup SH, Jensen TS. Efficacy of pharmacological treatments of neuropathic pain: An update and effect related to mechanism of drug action. *Pain* 1999; 83:389-400.
129. Kanpolat Y, Savas A, Bekar A, Berk C. Percutaneous Controlled radiofrequency trigeminal rhizotomy for the treatment of idiopathic trigeminal neuralgia: 25 years experience with 1600 patients. *Neurosurgery* 2001;48:524-534.
130. Geurts J, van Wijk RM, Stolker R, Groen GJ. Efficacy of radiofrequency procedures for the treatment of spinal pain: A systematic review of randomized clinical trials. *Reg Anesth Pain Med* 2001;26:394-400.
131. Slappendel R, Crul BJ, Braak GJ, et al. The efficacy of radiofrequency lesioning of the cervical spinal dorsal root ganglion in a double blinded randomized study: No difference between 40 degrees C and 67 degrees C treatments. *Pain* 1997;73:159-163.
132. Niemisto L, Kalso E, Malmivaara A, et al. Radiofrequency denervation for neck and back pain. A systematic review of randomized controlled trials. *Cochrane Database Syst Rev* 2003:CD004058.
133. Sluijter ME, Cosman ER, Rittman WB II, van Kleef M. The effects of pulsed radiofrequency field applied to the dorsal root ganglion—A preliminary report. *Pain Clin* 1998;11:109-117.
134. Higuchi Y, Nashold BS, Sluijter ME, et al. Exposure of the dorsal root ganglion in rats to pulsed radiofrequency currents activates dorsal horn lamina I and II neurons. *Neurosurgery* 2002;50:850-856.
135. Van Zundert J, de Louw AJ, Joosten EA, et al. Pulsed and continuous radiofrequency current adjacent to the cervical dorsal root ganglion of the rat induces late cellular activity in the dorsal horn. *Anesthesiology* 2005;102:125-131.
136. Van Zundert J, Lamé IE, de Louw A, et al. Percutaneous pulsed radiofrequency treatment of the cervical dorsal root ganglion in the treatment of chronic cervical pain syndromes: A clinical audit. *Neuromodulation* 2003;6:6-14.
137. Fouyas IP, Statham PF, Sandercock PA. Cochrane review on the role of surgery in cervical spondylotic radiculomyelopathy. *Spine* 2002;27:736-747.
138. Persson LC, Carlsson CA, Carlsson JY. Long-lasting cervical radicular pain managed with surgery, physiotherapy, or a cervical collar. A prospective, randomized study. *Spine* 1997;22:751-758.
139. Jacobs W, Anderson P, Limbeek J, et al. Single or double-level anterior interbody fusion techniques for cervical degenerative disc disease. *Cochrane Database Syst Rev* 2004:CD004958.
140. Persson LC, Lilja A. Pain, coping, emotional state and physical function in patients with chronic radicular neck pain. A comparison between patients treated with surgery, physiotherapy or neck collar—A blinded, prospective randomized study. *Disabil Rehabil* 2001;23:325-335.
141. Saklatvala J. The p38 MAP kinase pathway as a therapeutic target in inflammatory disease. *Curr Opin Pharmacol* 2004;4:372-377.
142. Lazzeri M, Spinelli M, Beneforti P, et al. Intravesical infusion of resiniferatoxin by a temporary in situ drug delivery system to treat interstitial cystitis: A pilot study. *Eur Urol* 2004;45:98-102.
143. Mitchell VA, White DM, Cousins MJ. The long-term effect of epidural administration of butamben suspension on nerve injury-induced allodynia in rats. *Anesth Analg* 1999;89:989-994.
144. Gerner P, Nakamura T, Quan CF, et al. Spinal tonicaine: Potency and differential blockade of sensory and motor functions. *Anesthesiology* 2000;92:1350-1360.
145. Carter GT, Sullivan MD. Antidepressants in pain management. *Curr Opin Investig Drugs* 2002;3:454-458.
146. Feighner JP. Mechanism of action of antidepressant medications. *J Clin Psychiatry* 1999;60(Suppl 4):4-11; discussion 2-3.
147. Pancrazio JJ, Kamatchi GL, Roscoe AK, Lynch C 3rd. Inhibition of neuronal Na+ channels by antidepressant drugs. *J Pharmacol Exp Ther* 1998;284:208-214.
148. Strumper D, Durieux ME. Antidepressants as long-acting local anesthetics. *Reg Anesth Pain Med* 2004;29: 277-285.
149. Sudoh Y, Cahoon EE, Gerner P, Wang GK. Tricyclic antidepressants as long-acting local anesthetics. *Pain* 2003;103:49-55.
150. Sudoh Y, Cahoon EE, De Girolami U, Wang GK. Local anesthetic properties of a novel derivative, N-methyl doxepin, versus doxepin and bupivacaine. *Anesth Analg* 2004;98:672-676.
151. Fridrich P, Eappen S, Jaeger W, et al. Phase Ia and Ib study of amitriptyline for ulnar nerve block in humans: Side effects and efficacy. *Anesthesiology* 2004; 100:1511-1518.
152. Glorioso JC, Fink DJ. Herpes vector-mediated gene transfer in treatment of diseases of the nervous system. *Annu Rev Microbiol* 2004;58:253-271.