Neuropathic Low Back Pain

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In this discussion, we hope to advance a clinical approach to low back pain that is more in line with our modern understanding of neuropathic pain. We review the current understanding of normal and pathologic neuroanatomy of the lumbar spine and then outline how pathology in the different structures can lead to neuropathic pain and cause common pain patterns seen in clinical practice. We also detail the available treatments for neuropathic low back pain.

Introduction

Low back pain (LBP) is the most common presenting complaint in pain and orthopedic specialty practices and is the second most common symptomatic complaint in a primary care setting, with an annual prevalence of 15% to 20% in the United States [1]. The most common cause of acute LBP often is described as nonspecific and generally is considered to have a primarily mechanical etiology and thus not one of neuropathic origin. Although disc herniation often is classified as a type of mechanical LBP (Table 1), it is perhaps the only commonly recognized cause of acute LBP that has neuropathic features. Chronic LBP is even less well understood, especially given the high prevalence of abnormal findings on imaging in populations of individuals without pain [2]. In many ways, on a clinical level, we are still working with a model of spine-related pain that would not be alien to colleagues of Dr. Jason Mixter. In 1934, Mixter and Joseph S. Barr published an article on the intervertebral disc lesion as the source of sciatica in the *New England Journal of Medicine* [3]. However, because we have learned more over the past two decades about the neurophysiologic mechanisms of persistent pain, there has been a growing understanding about the neuropathic features associated with LBP, especially when the pain has become chronic.

The current definition of neuropathic pain as proposed by the International Association for the Study of Pain (IASP) is "pain initiated or caused by a primary lesion or dysfunction of the nervous system" [4]. Part of the problem with the proper classification of neuropathic LBP is that there is still debate regarding the IASP definition of neuropathic pain, which has been criticized by many as vague, particularly the "dysfunction" component, and too frequently assigned to chronic pain disorders for which there is a lack of a clear finding of nerve damage or injury [5••]. Woolf and Costigan [6] have defined the following key features of neuropathic pain:

> "The presence of a lesion, damage or disruption to some component of primary sensory neurons. The lesion may be in a peripheral nerve, the dorsal root ganglion or a dorsal root and may be the consequence of trauma, compression, tumor invasion, ischemia, inflammation, metabolic disturbances, nutritional deficits, cytotoxic agents and degenerative disorders."

However, there are a variety of clinical conditions that appear to have neuropathic features that do not in any obvious way involve injury or dysfunction of the peripheral nervous system, making a definitive diagnosis of neuropathic pain problematic. This is especially true in cases in which the persistence of the pain, at least theoretically, suggests that there have been pathologic neuroplastic changes in the central nervous system (CNS), despite the lack of visible signs of damage to the peripheral nervous system. Cases such as complex regional pain syndrome type 1 (reflex sympathetic dystrophy), fibromyalgia, irritable bowel syndrome, interstitial cystitis, and many cases of chronic LBP are often cited as being in this grey zone. However, as Bennett [7••] points out, prematurely excluding these types of cases because, based on our current limited understanding of the etiology of these pain conditions, we think they do not meet criteria for neuropathic pain may have adverse clinical implications, leading to apprehension in prescribing a helpful agent such as gabapentin for fibromyalgia or chronic LBP because there is no known nerve damage. The following criteria that may be used to define neuropathic pain and differentiate it from other types of pain without absolutely excluding clinical conditions in this grey zone could include the following:

1. Pain and abnormal sensory symptoms that persist beyond the normal healing period,
2. Presence, to a variable degree, of gross or subtle sensory neurologic findings, potentially manifest-

ing as the absence of normal sensation or the presence of abnormally heightened sensation or both,
3. Presence, to a variable degree, of other neurologic signs, including motor or autonomic dysfunction,
4. The presence of neuropathic pain also would not exclude the presence of other types of pain and pain mechanisms such as inflammatory pain or gross mechanical disruption of normal tissue, often called nociceptive pain.

Normal Anatomy of the Lumbar Spine

Musculoskeletal anatomy

The lumbar spine links the thoracic vertebral column to the sacrum and consists of five separate lumbar vertebrae. Each vertebra consists of a vertebral body, three pairs of transverse processes, laminae and pedicles, and a spinous process. An intervertebral foramen is formed anteriorly by the posterior aspect of the vertebral body and disc, superiorly and inferiorly by the adjacent pedicles, and posteriorly by the respective facet joints. Each intervertebral disc consists of a centrally placed nucleus pulposus and a peripheral annulus fibrosus. The annulus is made up of strong collagen fibers that form highly ordered concentric rings surrounding the disc nucleus. Each lumbar facet joint is formed by a superior articular process of the caudally positioned vertebra and an inferior articular process of the overlying adjacent vertebra. This joint is a typical synovial joint consisting of an articular cartilage, synovium, and an encapsulating fibrous capsule.

An extensive ligamentous network adds extra stability to the lumbar spine. The vertebral bodies are held together by anterior and posterior longitudinal ligaments, which run vertically along the anterior and posterior aspects of the vertebral column, respectively. The lamina and the spinous processes are interconnected with the help of ligamentum flavum, interspinous, and supraspinous ligaments. A thick iliolumbar ligament connects the transverse processes of the L5 vertebra to the ilia. There is an impressive array of muscles surrounding the lumbar spine. Posteriorly, the erector spinae, multifidi, interspinales, and intertransversarii medialis muscles aid in lumbar rotation and extension.

Neural anatomy

The spinal cord, which typically terminates at the L2 vertebral level, sends out spinal nerves, which exit through their respective intervertebral foramina bilaterally. The typical spinal nerve is formed by the joining of a ventral and a dorsal root that occurs within the intervertebral foramen. The ventral root carries mainly motor fibers and the sensory root transmits sensory fibers from the spinal nerve to the spinal cord. Immediately before the junction with the ventral root, the dorsal root forms the dorsal root ganglion, which contains cell bodies of the root's ascending sensory fibers.

Table 1. Mechanical and nonmechanical causes of low back pain

Mechanical	Nonmechanical
Lumbar strain or sprain	Neoplasia
Spondylolysis or degenerative arthritis	Metastatic carcinoma
Degenerative disc disease	Multiple myeloma
Facet arthropathy	Lymphoma
Diffuse idiopathic skeletal hyperostosis	Spinal cord tumors
Spondylolysis	Retroperitoneal tumors
Spondylolisthesis	Infection
Herniated disc	Osteomyelitis
Spinal stenosis	Septic discitis
Osteoporosis with compression fracture	Paraspinal or epidural abscess
Fractures	Endocarditis
Severe kyphosis	Inflammatory arthritis
Severe scoliosis	Ankylosing arthritis
Paget's disease	Reiter's syndrome
Sacroiliac joint dysfunction	Psoriatic spondylitis
Myofascial pain	Inflammatory bowel disease
	Polymyalgia rheumatica

Upon exiting the intervertebral foramen, the spinal nerve splits into a ventral and a dorsal ramus. The ventral ramus eventually becomes part of the lumbosacral plexus, which provides motor and sensory innervation to the iliopsoas, gluteals, and muscles and skin of the lower extremity. The ventral ramus also sends off two other important branches, a grey rami communicantes, which connects the ventral ramus to the sympathetic trunk, and the sinuvertebral nerve, which re-enters through an intervertebral foramen and innervates the anterior structures of the central spinal canal. A dorsal ramus typically subdivides into three branches: medial, intermediate, and lateral. The lateral branch of the lumbar dorsal ramus innervates the skin and the underlying iliocostalis muscle [8,9]. The intermediate branch innervates the lumbar portion of the longissimus muscle [10,11]. The medial branch nerve innervates the multifidi facet joints and supra/interspinous ligaments [12] (Fig. 1).

The innervation of the intervertebral disk and the vertebral body periosteum is anatomically more complex. In a nonpathologic state, only the outer third of the annulus fibrosus carries sensory nerve endings [13]. The posterior aspect of the annulus and the adjacent periosteum are innervated by the posterior nerve plexus derived from the sinuvertebral nerves. The anterior nerve plexus formed by the two sympathetic trunks innervates the anterior annulus/periosteal complex [14]. Both of these plexi also are connected by a lateral nerve plexus, formed by the branches of grey rami communicantes, and innervate the lateral portion of the intervertebral disc and the vertebral body [15].

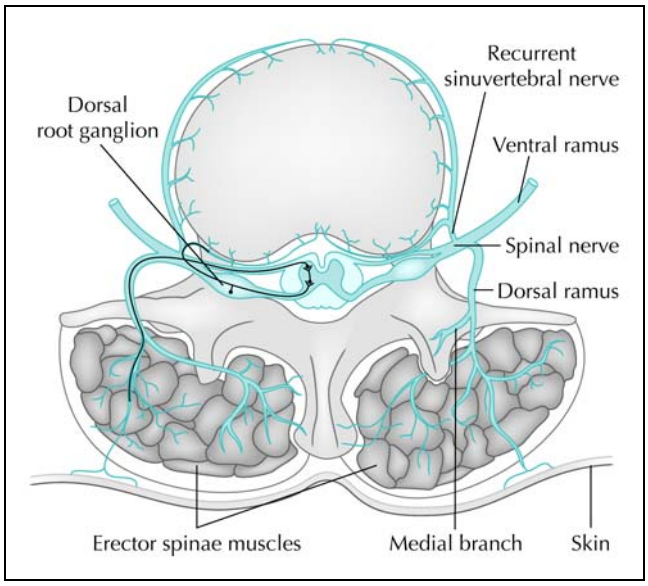

Figure 1. Normal neuroanatomy of the lumbar spine.

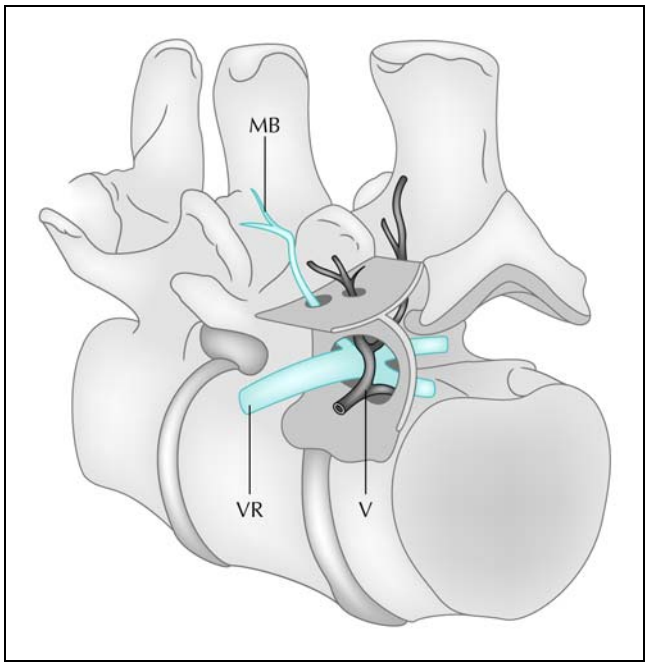

Figure 2. Illustration of the fascial planes through which the ventral ramus (VR) and medial branch (MB) of the dorsal ramus must pass in the extraforaminal space of the lumbar spine. V—vein.

Pathologic Anatomy of the Lumbar Spine

Entrapment neuropathy

Entrapment of nerve tissue at the spinal level can be subdivided into extraforaminal, intraforaminal, lateral recess, and central types. The putative mechanisms that lead to mechanical entrapment include microvascular ischemia, venous congestion, and possible axonal injury of the nerves involved. Secretion of inflammatory neuropeptides from degenerated discs and facet joints can lead to further sensitization and lowering of the pain threshold of the nerves and dorsal root ganglia involved. In addition, the nervi nervorum constitute the intrinsic innervation of nerve sheaths. There is evidence in animal models that even when the mechanical or chemical irritation is insufficient to sensitize the large nerve trunk, it can be sufficient to cause alteration in the sensitivities of the nervi nervorum and result in an entrapment neuropathy and the development of neuropathic pain along that segment [16,17].

As a result, the causes of extraforaminal entrapment neuropathy of the exiting spinal nerve may be caused by major mechanical derangement of the normal anatomy of the spine, including far lateral intervertebral disc protrusions (herniations), facet joint cysts, or hypertrophic facet joints, and by more subtle degenerative changes that may affect the nervi nervorum (Fig. 2).

An intraforaminal entrapment neuropathy can affect the exiting spinal nerve and the dorsal root ganglion and is caused by the pathologic narrowing of the involved neuroforamen. Common causes of this type of entrapment include facet joint pathology, intraforaminal disc protrusion, severe degenerative disc disease, and a high-level spondylolisthesis.

Structural narrowing of the lateral recess (lateral recess entrapment neuropathy) can involve the exiting spinal nerve, a descending spinal nerve that exits at the level below, or a combination of both. This can be caused by a paracentral focal disc protrusion, a large diffuse disc bulge, facet joint hypertrophy, facet joint cyst, spondylolisthesis, or a ligamentum flavum hypertrophy.

Depending on the level of a central entrapment neuropathy, the nerve tissue of the conus medullaris, which is the distal part of the spinal cord terminating at the L2 vertebral level, or the nerve roots of the cauda equina can be affected. The most common central entrapment neuropathy is of the degenerative type, which clinically presents as neurogenic claudication or spinal stenosis. A combination of hypertrophic facet joints, thickening of the ligamentum flavum, and degenerative protrusion of the intervertebral disc most commonly cause this structural entrapment. Other possible etiologies are spondylolisthesis and congenital narrowing of the central canal and the more ominous causes, including neoplasm, spinal abscess, or hematoma.

Neuropathic Discogenic Pain

In a normal intervertebral disc, only the outer portion of the annulus fibrosis receives sensory innervation. Histochemical studies of the degenerated discs have shown extensive nerve fiber in-growth into the middle third and even the inner third of the diseased annulus [18]. The nociceptive properties of at least some of these nerves have been suggested by the presence of substance P immunoreactivity [19]. A combination of the inflammatory neuropeptides within the degenerated disc together with

abnormal mechanical pressure loads experienced by an incompetent annulus can lead to chemical and mechanical sensitization and stimulation of these nerve fibers.

The Facilitated Segment

Peripheral nervous system

The neuroanatomy of nociception can be organized into three distinct but connected domains: the peripheral sensory apparatus, the spinal cord, and the brain. Starting in the periphery, small fiber sensory axons that respond to various types of noxious input are referred to as nociceptors. There are two main nerve types that carry pain and temperature information from cutaneous structures: the small, high-threshold unmyelinated C-fibers and the larger, thinly myelinated A-δ fibers. Similar sensory afferents are found in muscle; however, in muscle, thinly myelinated and unmyelinated fiber types (group III and IV) convey a dull aching sensation when activated in contrast to skin nociceptors. In addition to nociceptors responding to mechanical pain and temperature input, the release of chemical substances in damaged tissue such as protons, histamine, bradykinin, serotonin, vasoactive polypeptide, and a whole array of others also can lead to nociceptor sensitization [6].

Spinal cord

The sensory nerves from the periphery enter through the dorsal root ganglion and synapse primarily in laminas I through IV of the dorsal horn gray matter, with laminas I and II receiving the bulk of the nociceptive input from the skin and lamina IV and V from muscle. It is in lamina IV and V where wide dynamic range (WDR) second-order neurons reside. Unlike second-order neurons in lamina I and II, which have an on-off response to sensory input, the WDR neurons have a graded response to sensory input. Under pathologic conditions, wind-up can occur in the second-order WDR neurons found in lamina IV and V and low frequency input can lead to high frequency output. This heightened firing pattern of WDR neurons in the CNS is thought to be one of the factors involved with chronic pain [20]. Another unique feature of WDR second-order neurons is that there is convergence of sensory information from the afferents of skin, muscle, viscera, tendons, and joints [21]. This opens the door to understanding how persistent afferent drive from one damaged structure or sensitized nerve in the segment (*eg*, a facet joint or an entrapped medial branch nerve as it passes through scarred or shortened fascia) can cause neuroplastic changes in a WDR neuron that also receives input from the skin and muscle in that segment. The presence of a facilitated WDR neuron, fueled by the afferent drive of an underlying joint injury or subtle nerve entrapment, then can help to explain the common clinical finding in cases in which minimal sensory stimulation of skin (allodynia or hyperalgesia) or muscle (myofascial irritability) in the region of the facet can produce an exaggerated pain response, even when there has been no direct injury to that tissue.

Chronic Pain

Current research suggests that chronic pain may be the result of pathologic neuroplastic changes of the peripheral and central nervuous system. Changes in intracellular signal transduction, gene expression, receptor and ion channel density, and depolarization thresholds contribute to a peripheral sensitization and central wind-up phenomenon in the pain pathway. In addition, chronic damage, irritation, or facilitation of a sensory neuron at any point, even at the level of the dorsal horn, can lead to the retrograde release of neurotransmitters such as substance P and calcitonin gene-related peptide into peripheral tissue such as skin and muscle. This "neurogenic inflammation" in theory can cause a cascade of chemical releases that inappropriately signal tissue "damage" or "inflammation," which in turn can act in a feed forward manner to increase the peripheral and central facilitation of the sensory terminal [6]. Positive symptoms then can result from changes in the injured primary sensory neurons and in segmentally related non-injured tissues affecting multiple structures in that segmental level. Eventually, this facilitation can spread the longer such abnormalities persist, leading to trans-synaptic changes in neurons at multiple segments and levels of the CNS, causing more widespread pain [22].

Clinical Causes of Neuropathic Low Back Pain

Neuropathic pain of muscle origin

Myofascial pain syndrome (MPS) is a common, yet often under-recognized presenting cause of chronic LBP. The pain associated with MPS is thought to be due to the firing of low-threshold group-III and high-threshold group-IV muscle nociceptive afferents [21]. These nociceptors are thought to be activated by pH changes in the muscle due to transient ischemia [23]. However, this theory does not explain why many individuals without pain also have taut muscle bands, called latent trigger points, that would fit criteria for MPS, except that they lack pain at rest. One explanation is that the pain associated with an active trigger point depends on segmental central sensitization at the level of the spinal cord, which can lead to pain at rest and abnormal muscle irritability [24]. Recent work at the National Institutes of Health using an in vivo microdialysis technique suggests that the discomfort felt with active muscle trigger points is due to the release of neuropeptides into the muscle by the muscle nociceptors, which is called neurogenic inflammation [25]. In the absence of direct trauma to the muscle, the best explanation for the presence of neurogenic inflammation in the muscle would be the presence of a facilitated segment where the primary lesion is in a segmentally related structure such as a facet, disc, or related nerve entrapment.

Annular tears
Annular tears are the most common cause of minor sciatica and usually are the result of trauma to the spine and usually undergo spontaneous resolution after approximately 24 to 30 weeks. However, in a small number of patients, these tears do not resolve and progress to a state of chronic degenerative disc disease. Annular tears may lead to the leakage of a multitude of inflammatory mediators (*eg*, phospholipase A2) from the center of the involved discs into the epidural space, with the subsequent induction of an inflammatory response around the exiting adjacent spinal nerve roots causing neuropathic pain [26]. Signs of nerve dysfunction include positive sciatic dural tension signs (slump test or straight leg raising test) along with minor numbness and weakness along the dermatomal territory of the affected nerve. Given that there is no mechanical spinal irritation of the nerve, profound weakness or bladder and bowel dysfunction are extremely rare.

Disc prolapse
Disc prolapse results from central nuclear material herniation through a disrupted posterior annulus into the epidural space. Depending on the size, position, and the number of levels involved, there may be single or multiple spinal roots compressed. Significant central disc herniations can produce myelopathy by direct compression of the spinal cord if above L2 or bladder, bowel, and sexual dysfunction (and a saddle anesthesia) by compression of the sacral nerve roots and should be emergently evaluated. Foraminal disc extrusion describes the extrusion of disc material laterally into the neural foramen. This is quite uncommon and represents only approximately 5% to 10% of all disc herniations. An adverse consequence of a disc herniation into the neural foramen includes the interruption of the nutritional supply to the disc, with resultant fibrosis and more rapid degeneration.

Spinal stenosis
The normal lumbar canal diameter is more than 12 mm in the AP plane and more than 77 mm^2 in the cross-sectional area. When there is a 50% reduction in the cross-sectional area in animal models, motor and sensory deficits are produced. A diameter of less than 10 mm represents absolute stenosis [27]. Spinal canal stenosis may be congenital, but is most commonly of the acquired variety that is secondary to a variety of age-related factors, including progressive degenerative changes. Congenitally short pedicles are associated with the development of the acquired form of spinal stenosis earlier in life. Spondylolisthesis, post-surgical scarring, and Tarlov's cysts are less common causes of acquired spinal stenosis [28]. The mechanism of pain is thought to be due to neurogenic claudication by mechanical irritation and ischemia of the nerves as they exit the narrowed canal.

Foraminal stenosis
Foraminal stenosis is the narrowing of one or more neural foramina in the spine. Symptoms may be associated with axial- or sciatic-type back pain, particularly after prolonged standing or walking, due to gravity-related settling in the spine, leading to a decrease in the foraminal diameter. Neuropathic pain develops from nerve root irritation with referral to the buttocks or leg. Facet joint arthritis, osteophytosis, degenerative disc disease with loss of disc height, and spondylolisthesis are associated features of this source of back pain, which is not uncommon.

Spondylolisthesis
This is most common in the lumbar spine and is usually caused by a defect in the pars interarticularis. There are five grades described based on the percent of vertebral slippage: Grade 1 (< 25% displacement of vertebral body), Grade 2 (25% to 50% displacement of vertebral body), Grade 3 (50% to 75% displacement of vertebral body), Grade 4 (75% to 100% displacement of vertebral body), and Grade 5 (spondyloptosis) [29]. Acquired causes include acute trauma or fatigue fractures through the pars interarticularis and severe degenerative changes secondary to bilateral facet arthropathy (more commonly seen in elderly patients).

Spondylolysis
Spondylolysis, or a defect in the pars interarticularis, is thought to result from a combination of "weak" or poorly mineralized bone and repetitive trauma during the growth spurt. Predisposing familial conditions for spondylolysis include Marfan syndrome, osteogenesis imperfecta, osteopenia, spina bifida occulta, scoliosis, Scheuermann disease, and other inherited conditions. Participation in gymnastics, weight lifting, wrestling, and football at an early age with repetitive exposure to rotation, flexion-extension, and hyperextension often can cause fracture of the pars interarticularis.

Lumbar facet arthropathy
Lumbar facet arthropathy describes osteoarthritis of the lumbar apophyseal synovial joints and is virtually universal after the age of 60 years. Pain can be related to potential irritation of nervi nervorum from the medial branch nerve of the dorsal primary ramus, capsular distension, inflammatory synovitis, entrapment of synovial villi between two articular processes, or actual nerve impingement by osteophytes. Pain is centered in the hips, buttocks, or thighs, but at times can extend below the knees and typically is aggravated by hyperextension [30,31]. Facet arthropathy may be associated with synovial cysts, degenerative disc disease, and canal stenosis.

Epidural adhesions
Epidural adhesions and arachnoiditis can develop after spinal surgery and infections of the meninges, leading to adhesions that form around the lumbar spinal nerve roots, causing chronic irritation and sciatica. There is no correlation between the extent of surgery and the amount or

density of adhesions formed. Ionic water-based contrast agents used for antecedent myelography is associated with adhesions. The most common presentation is that of chronic LBP and radicular or nonradicular leg pain, which may simulate spinal stenosis and polyneuropathy.

Piriformis syndrome

Piriformis syndrome is a commonly underdiagnosed cause of buttock pain and sciatica caused by the compression and irritation of the sciatic nerve by the piriformis muscle.

The piriformis muscle originates at the sides of the sacral bone and inserts on to the posterior part of the greater trochanter of the femur. It externally rotates the leg with the leg straight and abducts the hip with the hip bent at 90 degrees. The sciatic nerve may pass through the piriformis muscle in 10% of the population and becomes compressed with contraction and shortening of the muscle. This is one of a number of MPSs that can cause LBP.

Referred pain

Referred pain can come from pathology in structures other than discs and nerves such as the zygapophysial joints, sacroiliac joints, hip joint and muscles, spinal paravertebral muscles, and spinal ligaments. Referred pain often presents as deep buttock or leg ache, sometimes with mild tingling, but rarely with any of the other sensory or motor signs of nerve dysfunction such as numbness, allodynia (pain caused by a stimulus that does not normally provoke pain such as light touch), hyperalgesia (an increased response to a stimulus that is normally painful, such as pinprick or hot sensation), or weakness. It occurs because the nerve supply to the area of reference and that of the culprit pain generator shares embryologic origins.

Clinical Diagnosis of Neuropathic Low Back Pain

Evaluation of an individual with suspected neuropathic LBP must include a detailed medical history and review of systems in addition to a comprehensive physical and neurologic examination to exclude primary peripheral neuropathies [32•]. The patient may report positive sensory symptoms such as tingling or burning pain and negative sensory symptoms such as numbness. Psychologic comorbidity and psychosocial stressors should be assessed to ensure the formulation of an optimal treatment plan. Functional and quality-of-life assessment should be made to guide treatment goals.

Examination of Neuropathic Low Back Pain

Sensory, motor, and autonomic dysfunction should be thoroughly investigated during the physical examination. When performing the sensory component of the examination for neuropathic LBP, special attention should be focused on the leg, inguinal region, gluteal region, and back. Segmental facilitation often is best assessed along the spine starting from the L1 dermatome just lateral to the spinous processes and working down the back to the sacral foramen. To properly assess the range of peripheral nerve dysfunction, light touch, pinprick, temperature, and vibration sensation should be assessed. There often can be sensory deficits with one modality such as loss of pinprick sensation and exaggerated positive responses to another modality such as pain with light touch. To help distinguish symptom amplification from reliable sensory dysfunction, there should be clear and repeatable findings in the affected area while the subject is able to respond normally in an unaffected area. In addition to findings of allodynia and hyperalgesia, one can look for signs of cutaneous C-fiber dropout by applying hot water in a plastic bag over the skin and comparing the time it takes to withdraw with an unaffected area. With the loss of C-fibers, the withdrawal latency will be prolonged. Summation also can be assessed by repeatedly applying the same pinprick stimulus with the same force and having the patient report the changing pain intensity. The normal nervous system tends to accommodate to repeated painful stimuli, whereas an individual with a facilitated nervous system may report increasing pain intensity. Other findings of autonomic dysfunction such as abnormal skin temperature, local areas of cutaneous trophedema, and hair loss should be checked. In addition to weakness, muscle irritability in a specific myotome, including trigger points, spontaneous muscle fasciculations, and cramps, also should suggest more subtle segmental nerve dysfunction. If abnormal sensory or motor findings are found along a certain dermatome or myotome, the corresponding dermatome along the spine segments should be checked for hyperalgesia and allodynia. Strong correlation between the distal and proximal abnormal sensory and motor findings is more supportive of specific segmental nerve root dysfunction and facilitation.

Treatment of Neuropathic Low Back Pain

Treatment should focus on treating the whole person, not just the pain problem. The goal should be to optimize the patient's chances of making a functional recovery in rehabilitation by improving exercise tolerance, mood, and sleep with the use of appropriate invasive and other nonpharmacologic therapies when appropriate [33] (Table 2). In general, when the pain is chronic, a biobehavioral approach is essential and cognitive-behavioral treatments should be viewed as important complements to the various treatments listed [34]. Medications play an essential role in the treatment of neuropathic LBP and the following principles should be applied:

1. Minimize side effects,
2. Minimize medications that could cause dependency issues,

Table 2. Common nonpharmacologic treatment options

Condition	Treatment options	Comments
Annular tears, disc prolapse, spondylolisthesis, and epidural adhesions		Treatment varies depending on presence or absence of radicular symptoms
	Spine exercises	Directional preference
	Thermal modalities	
	Epidural steroid injection	Transforaminal and interlaminar
	Chemonucleolysis	Used in Europe
	Intradiscal electrothermy	Poor evidence
	Percutaneous nucleoplasty	Poor evidence
	Spinal cord stimulation	
	Acupuncture/TENS therapy	For associated muscle spasm
	Spine surgery	
Spinal stenosis and foraminal stenosis	Spine exercises	Flexion preference
	Thermal modalities	
	Epidural steroid injection	Transforaminal and interlaminar
	Acupuncture/TENS therapy	For associated muscle spasm
	Spine therapy	
Facet arthropathy, segmental rigidity	Spine exercises	Directional preference
	Thermal modalities	
	Facet joint injections	If synovial cyst is present, percutaneous aspiration and steroid injection is indicated
	Radiofrequency ablation	If medial branch blocks are successful
	Transforaminal epidural	If nerve root impingement or irritation is suspected
	Joint manipulation	
	Acupuncture/TENS therapy	For associated muscle spasm
	Spine surgery	
Epidural adhesions, failed back syndrome	Transforaminal epidural	
	Lysis of adhesions	Transforaminal and caudal approach
	Spinal cord stimulation	
Vertebral compression fractures	Vertebroplasty	
	Thermal modalities	
Piriformis syndrome and myofascial pain	Stretching and strengthening program	
	Thermal modalities	
	Trigger point injections	
	Botulinum injections	
	Transforaminal epidural	If segmental facilitation is suspected
	Facet of sacroiliac joint	If underlying joint dysfunction is suspected
	Manipulation or injection	
	Acupuncture/TENS therapy	
Sacroiliac joint dysfunction	Stabilization exercises	
	Joint manipulation	
	Joint injection	

TENS—transcutaneous electrical nerve stimulation.
Data adapted from Nachemson and Jonsson [33].

3. Avoid cognitive impairment,
4. Avoid organ toxicity, and
5. Use rational polypharmacy when appropriate directed at different components of the pain.

When choosing medications, familiarity with the type of neuropathic pain and the basic mechanisms of actions of the various drug choices can provide some structure to treatment [35]. For example, better medication selection can be made if one can use, within reason, clinical findings and history to distinguish whether an individual has one or a combination of the following:

1. Sensitized peripheral nociceptor (the presence of hyperalgesia),
2. Altered central processing of pain or the wind-up phenomenon (summation of sensory input),

Table 3. Drug treatment for neuropathic pain

Drug	Starting dose	Dose range	Usual dose schedule	Major drug class and drug-specific characteristics and issues
Antidepressants				
TCAs				Prolonged QT interval, urinary retention, sedation
Amitriptyline	10 mg	10–150 mg	Once in the evening	More AEs
Nortriptyline	10 mg	10–150 mg	Once in the evening	Moderate AEs
Desipramine	10 mg	10–150 mg	Once in the evening	Fewer AEs
Selective serotonin norepinephrine reuptake inhibitors				
Venlafaxine	37.5 mg	150–375 mg	Once or twice daily	
Duloxetine	20 mg	40–60 mg	Once or twice daily	
SSRIs				Serotonin syndrome, impotence
Paroxetine	10 mg	20–60 mg	Once daily	
Citalopram	10 mg	20–60 mg	Once daily	
Other				
Bupropion	100 mg	200–400 mg	Once or twice daily	Agitation, tachycardia, seizures
Anticonvulsants				All cause some degree of cognitive impairment
Carbamazepine	200 mg	1000–1600 mg	Twice daily	Highly protein-bound, liver metabolism (AEs: aplastic anemia, hepatic)
Oxcarbazepine	300 mg	1200–2400 mg	Twice daily	Moderately protein-bound, liver metabolism (AEs: leukopenia, thrombocytopenia)
Valproic acid	250 mg	500–1000 mg	Twice daily	AEs: hepatic failure, thrombocytopenia, pancreatitis
Phenytoin	100 mg	300–500 mg	Once daily	AEs: gum hypertrophy, osteomalacia, lymphadenopathy, hepatoxicity, blood dyscrasias
Gabapentin	100 mg	1800–3600 mg	Three or four times daily	< 3% protein bound, not metabolized (AE: cognitive)
Lamotrigine	25 mg	200–600 mg	Once or twice daily	Moderately protein-bound, liver metabolism (AEs: Stevens-Johnson syndrome, paresthesias)
Topiramate	25 mg	100–800 mg	Once or twice daily	17% protein-bound, minimal liver metabolism (AEs: cognitive, renal stones, glaucoma)
Levetiracetam	250 mg	1000–3000 mg	Once or twice daily	< 10% protein-bound, minimal liver metabolism (AE: cognitive)
Tiagabine	2 mg	4–56 mg	Two to four times daily	Highly protein-bound, liver metabolism (AEs: cognitive, may improve sleep architecture)
Clonazepam	0.5 mg	1.5–20 mg	One to three times daily	AEs: cognitive, blood dyscrasias
Antiarrhythmic				
Mexiletine	150 mg	300–1200 mg	Twice daily	AEs: gastrointestinal, hepatic, arrhythmia
α-2 agonist				Hypotension, sedation
Clonidine	0.1 mg	0.3–2.4 mg	One to three times daily	Hepatic
Tizanidine	2 mg	8–36 mg	One to three times daily	Hepatic
Analgesics				
Tramadol	50 mg	150–400 mg	Three or four times daily	Risk of serotonin syndrome with use of SSRIs, TCAs
Opioids	5–10 mg	30–188 mg	Varies	Somnolence, constipation, mood alterations, risk of tolerance and dose escalation
Topical agents				

AEs—adverse events; SSRIs—selective serotonin reuptake inhibitors; TCAs—tricyclic antidepressant.

Table 3. Drug treatment for neuropathic pain *(Continued)*

Drug	Starting dose	Dose range	Usual dose schedule	Major drug class and drug-specific characteristics and issues
Lidocaine 5% patch		Up to 3 patches	12 hours	Potentiates cardiac toxicity from mexiletine
Capsaicin 0.075%		Up to 3 patches	Three times daily	Rash
Doxepin 5%		Up to 3 patches	Three times daily	Potential systemic side effects similar to TCAs

AEs—adverse events; SSRIs—selective serotonin reuptake inhibitors; TCAs—tricyclic antidepressant.

3. Loss of descending pain modulation and loss of inhibitory neurons in the dorsal horn with C-fiber dropout and phenotypic switching of A-β fibers (allodynia, segmental widening of pain, and/or bilateral findings), and
4. Altered sympathetic activation (trophedema, temperature changes).

With this approach, a patient with signs and symptoms suggestive of neuropathic pain that fit into category 1 above may respond better to a topical lidocaine patch, mexiletine, or an anticonvulsant with known sodium channel-blocking properties, such as topiramate or lamotrigine, rather than gabapentin. Individuals with neuropathic pain that fits into category 3 may respond better to antidepressants and may have little or no response to a topical patch. In general, most patients will manifest with some combination of the four classes; therefore, rational polypharmacy often makes sense. Table 3 lists the medications available for the treatment of neuropathic pain. Of those listed, only the tricyclic antidepressants, gabapentin, tramadol, topical lidocaine 5%, and opioids have strong support in the literature for effectiveness [35]. The others listed have the promise of potential benefit with case reports or a single randomized, controlled trial to support their use [32•,36]. A thorough discussion of the use of opioids for neuropathic pain can be found elsewhere [37–39,40•].

Conclusions

The treatment of LBP can be challenging partly because of the lack of a clear theory about the causes, especially when the pain has become chronic. Although biobehavioral- and rehabilitation-based therapies are important, in many cases, patients fail to make progress because of unremitting, functionally limiting pain. Based on the previous discussion, we hope that clinicians will become more aware that neuropathic pain often is present in LBP and with appropriate assessment and treatment; early institution of appropriate treatment could prevent the devastation of severe persistent neuropathic pain.

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