Understanding Neuropathic Pain
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Introduction
Pain is usually the natural consequence of tissue injury resulting in approximately forty million medical appointments per year. In general, as the healing process commences, the pain and tenderness associated with the injury will resolve. Unfortunately some individuals experience pain without an obvious injury or suffer protracted pain that persists for months or years after the initial insult. This pain condition is usually neuropathic in nature and accounts for a large number of patients presenting to pain clinics with chronic, non–malignant pain. Rather than the nervous system functioning properly to sound an alarm regarding tissue injury, in neuropathic pain the peripheral or central nervous systems are malfunctioning and become the cause of the pain.

Terminology
Acute pain and chronic pain differ in their etiology, pathophysiology, diagnosis and treatment. Acute pain is self–limiting and serves a protective biological function by acting as a warning of on–going tissue damage. It is a symptom of a disease process experienced in or around the injured or diseased tissue. Associated psychological symptoms are minimal and are usually limited to mild anxiety. Acute pain is nociceptive in nature, and occurs secondary to chemical, mechanical and thermal stimulation of A–delta and C–polymodal pain receptors.

Chronic pain, on the other hand, serves no protective biological function. Rather than being the symptom of a disease process, chronic pain is itself a disease process. Chronic pain is unrelenting and not self–limiting and as stated earlier, can persist for years and even decades after the initial injury. Chronic pain can be refractory to multiple treatment modalities. If chronic pain is inadequately treated, associated symptoms can include chronic anxiety, fear, depression, sleeplessness and impairment of social interaction. Chronic, non–malignant pain is predominately neuropathic in nature and involves damage either to the peripheral or central nervous systems.

Nociceptive and neuropathic pain are caused by different neuro–physiological processes, and therefore tend to respond to different treatment modalities. Nociceptive pain is mediated by receptors on A–delta and C–fibers which are located in skin, bone, connective tissue, muscle and viscera. These receptors serve a biologically useful role at localizing noxious chemical, thermal and mechanical stimuli. Nociceptive pain can be somatic or visceral in nature. Somatic pain tends to be well localized, constant pain that is described as sharp, aching, throbbing, or gnawing. Visceral pain, on the other hand, tends to be vague in distribution, paroxysmal in nature and is usually described as deep, aching, squeezing and colicky in nature. Examples of nociceptive pain include: post–operative pain, pain associated with trauma, and the chronic pain of arthritis. Nociceptive pain usually responds to opioids and non–steroidal anti–inflammatories (NSAIDS).

Neuropathic pain, in contrast to nociceptive pain, is described as "burning", "electric", "tingling", and "shooting" in nature. It can be continuous or paroxysmal in presentation. Whereas nociceptive pain is caused by the stimulation of peripheral of A–delta and C–polymodal pain receptors, by algogenic substances (eg. histamine bradykinin, substance P, etc.) neuropathic pain is produced by damage to, or pathological
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Examples of pathological changes include prolonged peripheral or central neuronal sensitization, central sensitization related damage to nervous system inhibitory functions, and abnormal interactions between the somatic and sympathetic nervous systems. The hallmarks of neuropathic pain are chronic allodynia and hyperalgesia. Allodynia is defined as pain resulting from a stimulus that ordinarily does not elicit a painful response (eg. light touch). Hyperalgesia is defined as an increased sensitivity to a normally painful stimuli. Primary hyperalgesia, caused by sensitization of C–fibers, occurs immediately within the area of the injury. Secondary hyperalgesia, caused by sensitization of dorsal horn neurons, occurs in the undamaged area surrounding the injury.

Examples of neuropathic pain include: monoradiculopathies, trigeminal neuralgia, postherpetic neuralgia, phantom limb pain, complex regional pain syndromes and the various peripheral neuropathies. Neuropathic pain tends to be only partially responsive to opioid therapy.

Pathophysiology

The mechanisms involved in neuropathic pain are complex and involve both peripheral and central pathophysiologic phenomenon. The underlying dysfunction may involve deafferentation within the peripheral nervous system (eg. neuropathy), deafferentation within the central nervous system (eg. post–thalamic stroke) or an imbalance between the two (eg. phantom limb pain).

Peripheral Mechanisms:

Following a peripheral nerve injury (eg. crush, stretch, or axotomy) sensitization occurs which is characterized by spontaneous activity by the neuron, a lowered threshold for activation and increased response to a given stimulus. Should the injured nerve be a nociceptor then increased nervous discharge will equate to increased pain. Following nerve injury C–fiber nociceptors can develop new adrenergic receptors and sensitivity, which may help to explain the mechanism of sympathetically maintained pain.

In addition to sensitization following damaged peripheral nerves, the formation of ectopic neuronal pacemakers can occur at various sites along the length of the nerve. Increased densities of abnormal or dysfunctional sodium channels are thought to be the cause of this ectopic activity. The sodium channels in damaged nerves differ pharmacologically and demonstrate different depolarization characteristics. This may explain the rationale of treatment with lidocaine, mexiletine, phenytoin, carbamazepine, and tricyclic antidepressants each of which blocks sodium channels. These ectopic pacemakers can occur in the proximal stump (eg. neuroma), in the cell bodies of the dorsal root ganglion, and in focal areas of demylenation along the axon. Neuromas are composed of abnormal sprouting axons and have a significant degree of sympathetic innervation. Neuromas have been reported to accumulate sodium channels at their distal ends which can modulate their sensitivity. They can acquire adrenergic sensitivity, as indicated by increased pain following injection of norepinephrine into the neuroma. Neuromas can also acquire sensitivity to catecholamines, prostanoids and cytokines. Novel ion channels or receptors, not found in normal nerves, appear to be expressed in the regenerating terminal/axon.

Further animal investigations suggest that abnormal electrical connections can occur between adjacent demyelinated axons. These are referred to as ephapses. "Ephaptic cross talk" may result in the transfer of nerve impulses from one axon to another. Cross talk between A and C fibers develops in the dorsal root ganglion. Nerve growth trophic factors may be important in the elaboration of these changes. A similar event referred to as "crossed afterdischarge" has also been described whereby "the sprouts of primary
afferents with damaged axons can be made to discharge at high frequencies by the discharge of other afferents." It is also theorized that injured nerves may contain ephapses between sensory and sympathetic fibers, and such cross–connections may play a role in the pathogenesis of sympathetically mediated pain.

Neurogenic inflammation is a useful model for understanding pain and hyperalgesia. Neurogenic inflammation and the cascade of events following neural injury have been described. Inflammatory neuropeptides (substance P) and prostaglandins (PGE2) may be released from primary afferent nociceptors and sympathetic postganglionic neurons respectively activating nearby receptors and triggering a process of spreading activation. These mechanisms may explain the clinical response of some neuropathic pain patients to topical nonsteroidal anti–inflammatory drugs, lidocaine, and capsaicin.

The connective tissue sheath around peripheral nerves is innervated by the nervi nervorum. Injury, compression, and inflammation of the sheath may cause pain. In cancer patients, pain associated with tumor compression of neural structures is clinically indistinguishable from non–malignant neuropathic pain. This nervi nervorum related pain may resolve following tumor resection or treatment of tumor induced inflammation. Anti–inflammatory medications (NSAIDs and corticosteroids) have been shown to be effective in certain neuropathic pain conditions. The mechanism of pain relief may be decreased edema at the tumor or injury site. However these medications also have membranes stabilizing effects and central analgesic effects. Therefore it is extremely difficult to distinguish primary tumor–associated inflammation and involvement of the nervi nervorum from other mechanisms of neuropathic pain.

Central Mechanisms:

Following a peripheral nerve injury, anatomical and neuro–chemical changes can occur within the central nervous system (CNS) that can persist long after the injury has healed. This “CNS plasticity” may play an important role in the evolution of chronic, neuropathic pain. As is the case in the periphery, sensitization of neurons can occur within the dorsal horn following peripheral tissue damage and this is characterized by an increased spontaneous activity of the dorsal horn neurons, a decreased threshold and an increased responsivity to afferent input, and cell death in the spinal dorsal horn. In the non–injured state, A beta fibers (large myelinated afferents) penetrate the dorsal horn, travel ventrally, and terminate in lamina III and deeper. C fibers (small unmyelinated afferents) penetrate directly and generally terminate no deeper than lamina II. However, after peripheral nerve injury there is a prominent sprouting of large afferents dorsally from lamina III into laminae I and II. After peripheral nerve injury, these large afferents gain access to spinal regions involved in transmitting high intensity, noxious signals, instead of merely encoding low threshold information.

Significant alterations have been shown in the dorsal horn ipsilateral to the injury. The mechanisms are likely related to the barrage of afferent impulses or the factors transported from the lesion site. Studies have revealed that peripheral nerve injury may lead to increased mRNA for specific neurotransmitters (e.g. substance P), differential temporal expression of mRNA and receptors decreased levels of opioid binding sites appearance of immediate early gene products (e.g. c–fos) of which the significance is that peripheral nerve injury is causing changes in the cell’s synthesis of products, and alterations in the relative levels of neuropeptides/neuromodulators (e.g. increased galanin and VIP and reductions in sP and CGRP).

Several forms of thermal or tactile hyperalgesia may involve the intercellular and intracellular messengers nitric oxide and arachidonic acid and metabolites. Cyclooxygenase inhibition appears to suppress tactile allodynia. Blockade of activation of protein kinase C has been shown to prevent behavioral neuropathic manifestations. Protein kinase C removes the voltage gating of the NMDA receptor, allowing activation of the receptor by glutamate. Protein kinase C may also modulate sodium channels.

The injured axon may release factors which may be transported in a retrograde or orthograde fashion to initiate changes important to the development of a pain state. Thermal hyperalgesia has been prevented in the Bennett model of nerve injury by blocking axonal transport bidirectionally with colchicine. It has been shown also that colchicine blocks orthograde transport of tachykinins which may explain its ability
to induce prolonged reductions in sciatic neurogenic extravasation at concentrations that spare C–fiber nociceptor function.

Repetitive noxious stimulation of unmyelinated C–fibers can result in prolonged discharge of dorsal horn cells. This phenomenon which is termed "wind–up", is a progressive increase in the number of action potentials elicited per stimulus that occurs in dorsal horn neurons. Repetitive episodes of "wind–up" may precipitate long–term potentiation (LTP), which involves a long lasting increase in the efficacy of synaptic transmission. Where "wind–up" is thought to last only minutes, LTP by definition, lasts at least one hour and maybe even months. Both "wind–up" and LTP are believed to be part of the sensitization process involved in many chronic pain states.

Animal studies suggest that expansion of receptive fields may also occur following tissue injury. Therefore, any peripheral stimulation would activate a greater number of dorsal horn cells because of an increased overlap of their receptive fields.

Evidence suggests that excessive nociceptive input to the dorsal horn can have excitotoxic consequences resulting in the death of inhibitory interneurons. This inhibition may contribute to spinal hyper–excitability.

The alldynia and hyperalgesia associated with neuropathic pain may be best explained by: 1) the development of spontaneous activity of afferent input 2) the sprouting of large primary efferents (eg. A–beta fibers from lamina 3 into lamina 1 and 2), 3) sprouting of sympathetic efferents into neuromas and dorsal root and ganglion cells, 4) elimination of intrinsic modulatory systems and 5) up regulation of receptors in the dorsal horn which mediate excitatory processes.

Recent animal studies have shown that dynamic and static hyperalgesia are probably mediated by different mechanisms, tactile allodynia and hyperalgesia are likely mediated by different mechanisms and repetitive thermal and mechanical stimuli are likely processed in different ways.

On a cellular level, the central nervous system plastic changes appear to be associated with enhanced neurotransmission via the NMDA receptor. Under the appropriate conditions, appropriate C–fiber stimulation can activate dorsal horn inter–neurons, causing them to release excitatory amino acids (eg. aspartate and glutamate), which will excite wide dynamic range (WDR) neurons via the NMDA receptor. Hanai found that the C fiber response to stimulation of the superficial peroneal nerve consisted of three components: early, middle, and late. The separation into three components was found to be caused by asynchronous volleys in three different classes of C fibers in the superficial peroneal nerve. The phenomenon of wind up was observed to occur always in the late component, frequently in the middle component and to a far lesser extent in the early component. The NMDA antagonist, MK801 significantly suppressed the middle and late components of the C fiber response, although the effect on the early component was insignificant. NMDA receptor activation triggers a cascade of events leading to sensitization of dorsal horn wide dynamic range neurons then ensues. There is a significant increase in intracellular calcium and activation of protein kinases and phosphorylating enzymes. NMDA receptor stimulation will also increase the production of spinal phospholipase and induce the production of nitric oxide synthetase. The prostaglandins and nitric oxide which are subsequently produced and released into the extracellular milieu can facilitate further release of excitatory amino acids and neuropeptides from primary afferent pain fibers. The NMDA receptor antagonists ketamine and dextromethorphan can block this cascade of events which contribute to sensitization.

**Management of Neuropathic Pain**

Early recognition and aggressive management of neuropathic pain is critical to successful outcome. Oftentimes, multiple treatment modalities are provided by an interdisciplinary management team. Numerous treatment modalities are available and include systemic medication, physical modalities (eg. physical rehabilitation), psychological modalities (eg. behavior modification, relaxation training), invasive procedures (eg. trigger–point injections, epidural steroids, sympathetic blocks), spinal cord stimulators, intrathecal
Morphine pump systems and various surgical techniques (e.g., dorsal root entry zone lesions, cordotomy and sympathectomy). It should be noted that caution is warranted regarding the use of neuroablative techniques. Such approaches may produce deafferentation and exacerbate the underlying neuropathic mechanisms. The focus of this review will be on pharmacological interventions.

As previously mentioned, most neuropathic pain responds poorly to NSAIDS and opioid analgesics. The mainstay of treatment are predominantly the tricyclic antidepressants (TCA's), the anticonvulsants and the systemic local anesthetics. Other pharmacological agents that have proven efficacious include the corticosteroids, topical therapy with substance P depleters, autonomic drugs and NMDA receptor antagonists.

The TCA's have been successfully used for the treatment of neuropathic pain for some 25 years. The mechanism of action for the alleviation of neuropathic pain is thought to be due to the inhibition of re-uptake of serotonin and norepinephrine within the dorsal horn, however, other possible mechanisms of action include alpha–adrenergic blockade, sodium channel effects and NMDA receptor antagonism.

 Amitriptyline is the prototypical tertiary amine. Other tertiary amines include imipramine, doxepine, clomipramine and trimipramine. Unlike the dosing regimen utilized for the treatment of depression doses of TCA's for treatment of neuropathic pain are considerably less. The typical dosing schedule for amitriptyline may be simply 10 mg orally at bedtime with a gradual escalation every three days, in 10 mg increments, to a maximum to 30 to 50 mg orally at bedtime. Furthermore, the onset analgesia usually occurs over several days versus the two weeks that are required for the onset of the antidepressant effects of the drugs.

The side effect profile of the TCA's include sedation and anticholinergic effects. Since these side effects are more prominent with the tertiary amines prudence would dictate the use of a secondary amine such as nortriptyline or desipramine, particularly in the elderly population who are more sensitive to the side effects.

The recently introduced selective serotonin reuptake inhibitors (SSRI's) have not proven to be as effective against neuropathic pain as anticipated. Fluoxetine (Prozac) only appears to relieve pain in patients with co–morbid depression. Paroxetine (Paxil) has found some utility in the treatment of chronic, daily headaches. In general, the SSRI's are partially effective in the treatment of diabetic neuropathy, but not to the extent of the TCA's. Venlafaxine (Effexor) may have some analgesic effects since, like the TCA's, it inhibits the reuptake of both serotonin and norepinephrine. Its side effect profile is similar to the other SSRI's and can include agitation, insomnia, or somnolence, gastrointestinal distress and inhibition of sexual functioning. Anticholinergic side effects are less bothersome than with the TCA's.

The anti–convulsant medications can be particularly effective treatment for neuropathic pain that is described as burning and lancinating in nature. Commonly used medications in this category include phenytoin, carbamazepine, valproic acid, clonazepam, and gabapentin.

Carbamazepine has proven to be particularly effective against glossopharyngeal neuralgia, post herpetic neuralgia, trigeminal neuralgia, and diabetic neuropathies. Should carbamazepine prove ineffective, it can be replaced with phenytoin. Unlike the other anticonvulsants, valproic acid has found some success in treating migraine headaches. The combination of an anticonvulsant with a TCA can be synergistic.

The mechanism of action of the anticonvulsant medications is thought to involve membrane stabilization. Evidence also suggests that some of the agents, such as carbamazepine and phenytoin can depress both segmental and descending excitatory pathways in the CNS and at the same time facilitate inhibitory mechanisms. For example, carbamazepine has been shown to inhibit the electrical C and A fiber evoked neuronal responses of spinal nerve ligated rats. Valproic acid, on the other hand, has been reported to increase gamma–amino butyric acid (GABA) levels in the substantia nigra and corpus striatum. Gabapentin, which we will be discussing subsequently, reportedly increases extracellular GABA levels throughout the brain, including the thalamus and causes the release of GABA from glial cells. However it is unlikely that
Gabapentin increases GABAergic tone because neither GABA_a nor GABA_b antagonists reverse the analgesic effects of Gabapentin.

Because of the significant risks of the blood dyscrasias and liver dysfunction, baseline and periodic monitoring of blood chemistries and liver function tests are highly recommended when prescribing phenytoin, carbamazepine, or valproic acid.

Although clonazepam, a benzodiazepine, is usually used for the treatment of petit mal and myoclonic seizures, it has been successfully utilized to treat the lancinating and pain associated with phantom limb pain. Its mechanism of action may be associated with its reputed ability to enhance the inhibitory action of GABA within the CNS, and also possibly secondary to increased serotonin levels.

Gabapentin (Neurontin), 1-(aminomethyl) cyclohexane–acetic acid, is an anti–epileptic drug which was introduced in 1993 and was originally approved for the treatment of partial seizures with or without secondary generalization. Recently, however, reports have documented its efficacy in the treatment of various neuropathic pain states such as complex regional pain syndrome, deafferentation neuropathy of the face, postherpetic neuralgia, sciatic type pain, and HIV–related neuropathy. The effective dose range is 30–300 mg/kg (systemic) and >37.5 mg/kg (IT). Gabapentin is reportedly completely ineffective in altering threshold responses to acute nociceptive stimuli at doses up to 300 mg/kg. Presently the mechanism of action as either an anticonvulsant or an analgesic is unknown. The antinociceptive effects are likely to be due to actions within the spinal cord, because 1000 times the IT dose is required to produce equianalgesic effects when given intraperitoneally. Gabapentin binds to the alpha 2 delta calcium channel subunit. However, the relationship between binding at this site and the analgesic properties of gabapentin have not been determined. The NMDA receptor complex may be a potential spinal locus for neuropathic pain relief, but it has not been conclusively found that this is the major site of action. Gabapentin has a relatively benign side effect profile and is well tolerated if dosing proceeds in a gradually escalating manner. It has few if any drug interactions and is primarily renally excreted. Although expensive, it does not require the routine monitoring of blood chemistries and liver functions tests like carbamazepine and phenytoin. To date, little evidence suggests the efficacy of felbamate or lamotrigine in the treatment of neuropathic pain. Further investigation is necessary.

The systemic local anesthetics which are commercially available include lidocaine, tocainide, and mexiletine. The assumed mechanism of action to effect analgesia is the acute blocking of sodium channels. Phenytoin, carbamazepine and tricyclic antidepressants also act as sodium channel blockers. Following the use of the TCA's and anticonvulsants, local anesthetics tend to be third line drugs. Lidocaine has proven effective for noncancer patients but not for those with cancer. In cancer patients tumor involvement of nervi nervorum with "nociceptive neuropathic pain" (as discussed earlier) may represent a different mechanism with variable response to therapy. The predictive value of lidocaine in determining the expected benefits of drugs such as mexiletine remains important in allowing us to move more efficiently through therapeutic trials. Recent studies have suggested that the duration and pattern of spontaneous discharge is dependent on the level and kinetics of Na+ slow channel inactivation. Slow inactivation of voltage–gated ion channels could be major factors in the induction and treatment of neuropathic pain. QX–314, a positively charged lidocaine derivative which is frequently assumed to be membrane impermeant, has recently been shown to acutely block Na+ channels at nerve injury sites in rats. We avoid the use of tocainide because of unacceptable side effects which include blood dyscrasias and pulmonary fibrosis. Dosing of mexiletine is begun at 150 mg po qd and is slowly escalated by 150 mg q 72 hours to a maximum of 10 mg/kg/day as tolerated. The only absolute contraindication to the use of mexiletine is pre–existing second or third degree AV block or known allergy to the medication.

Autonomic drugs which are proven beneficial in the treatment of neuropathic pain include the alpha–2 agonists (eg. Clonidine) and alpha–1 antagonists (eg. prazosin, terazosin). The role of the 2 adrenergic system in neuropathic pain has been studied using various pharmacologic interventions and animal models.63 In animal studies, alpha 2 adrenergic agonists produce analgesia by actions in the periphery, supraspinal CNS,
Spaulding et al studies in mice suggested a primary spinal site of action. Clonidine is believed to produce analgesia at the spinal level in part through stimulation of cholinergic interneurons in the spinal cord. This cholinergic mediation of analgesia, as reflected by CSF acetylcholine concentration is activated by intrathecal, but not IV, injection of clonidine. However, clonidine has been shown to produce analgesia to experimental pain stimuli after systemic and epidural injection. Yet, clinical studies of systemic clonidine for analgesia have yielded conflicting results. Alpha 2 adrenergic agonists produce sedation and reduced blood pressure in addition to analgesia small doses (ie 50 mg) clonidine may reduce blood pressure more after an intrathecal than IV injection. Clonidine has also been shown to potentiate the neuropathic pain relieving action of NMDA antagonist MK–801 while preventing its neurotoxic and hyperactivity side effects. Clonidine is available in several different dosage forms and can be administered orally, transdermally or spinally. Conversely, systemic Dexmedetomidine, another alpha 2 adrenergic agonist, has been shown neither to prevent nor attenuate neuropathic pain behavior in rats.63 Dexmedetomidine has affinity to all three alpha 2– adrenergic subtypes. The role of the different subtypes of alpha 2 adrenoreceptors is unclear. Subtype–selective alpha 2–adrenergic agonists are needed for further studies.

Several other pharmacological treatments which have proven beneficial in the treatment of neuropathic pain include the corticosteroids, and capsaicin cream. Corticosteroids are believed to provide long–term pain relief because of their ability to inhibit the production of phospholipase–A–2 and through membrane stabilizing effects, hence their utility for epidural steroid injections. Topical capsaicin cream (Zostrix, 0.025% and 0.075%) is a substance P depletor, and has on occasion provided relief for both acute herpetic neuralgia (shingles) and post–herpetic neuralgia. Capsaicin is known for its selectivity for and effect on C–fiber nociceptors and heat receptors. Studies have shown its ability to trigger membrane depolarization and to open non selective cation channels, which may be either reversible or lytic. Capsaicin is theorized to cause a neurotoxic cellular degeneration of primary afferent nociceptors. Basically, exposure to capsaicin results in activation, desensitization, and under certain conditions, the destruction of lightly myelinated or unmyelinated primary afferent fibers. A recent preliminary study proposes a clinical role for topical capsaicin at doses of 5%–10% in patients with intractable pain. A recent animal study suggests that an orally bioavailable capsaicin analogue, civamibe (cis–8–methyl–N–vanillyl–6–nonenamide) possessed analgesic activity with respect to several noxious stimuli, including nerve injury–induced tactile allodynia. Compliance may be a problem with this medication, since it needs to be applied 4–5 times a day for several weeks before any significant benefit is appreciated and it has intense initial burning effects. A recent study demonstrated that if famciclovir (Famvir) is administered within 72 hours of the onset of the vesicles of shingles then damage to peripheral nerves can be minimized and therefore, the subsequent pain of post–herpetic neuralgia attenuated. The dose of famciclovir is 500 mg orally, three times a day for seven days.

If a chronic neuropathic pain condition is already well established, treatment is more difficult. Sensitization (eg. “wind–up”) is presumed to have already occurred, so the ideal medication would include an NMDA receptor antagonist. Two agents are currently available. Ketamine is an injectable anesthetic that non–competitively antagonizes NMDA receptors. Although it has proven beneficial in the treatment of neuropathic pain, side effects tend to be unacceptable. NMDA receptor antagonists are known to induce psychomimetic reactions in adult humans and induce behavioral disturbances such as learning and memory impairments, sensorimotor disturbances, stereotypical behavior and hyperactivity and pathomorphological changes in neurons of the posterior cingulate/retrosplenial (PC/RS) cortex of the adult rat. Recent animal studies have reported that preemptive intrathecal ketamine delayed mechanical hyperalgesia but did not prevent it. Also, a case report suggests that epidural administration of a "very low dose" of Ketamine is sufficient to block activated NMDA receptors and is an effective choice for the management of neuropathic pain without undesirable side effects. We occasionally will prescribe dextromethorphan, a readily available over–the–counter antitussive, to supplement the medication regimen of some of our patients with neuropathic pain. Like Ketamine, it is a non–competitive antagonist at the NMDA receptor. However in humans, doses may be so high that unacceptable side effects occur. MK801, an antagonist for the N–methyl–D–aspartate receptor for glutamate, has been shown to reverse mechanical hyperalgesia in streptozotocin/ diabetic rats and conversely to have no effect on tactile allodynia in nerve–injured rats. Amantadine, an antiviral and anti Parkinsonian agent, was shown to act as a non–competitive NMDA antagonist. Unlike
other NMDA antagonists amantadine is clinically available for chronic use in humans and its level of toxicity is low. Case reports and a preliminary double blind, controlled trial show that acute administration of amantadine significantly reduces surgical neuropathic pain in cancer patients. Investigational NMDA receptor antagonists are currently undergoing clinical trials.

Activation of NMDA receptors leads to calcium entry into the cell and initiates a series of central sensitization. This sensitization may be blocked not only with NMDA receptor antagonists, but also with calcium channel blockers that prevent Ca2+ entry into cells. A double blind study revealed that epidural verapamil and bupivacaine reduced the amount of self administered post op analgesics versus epidural bupivacaine alone. The authors suggest that epidural verapamil may prevent central sensitization by surgical trauma.

Clinical experience with the use of opioids for chronic non–malignant pain which is neuropathic in character suggests that there may be a sub–population of chronic pain patients who may clearly benefit from maintenance with opioid analgesics. Many studies have shown that neuropathic pain is only slightly responsive or not responsive at all to opioid treatments. Yet others have shown that neuropathic pain responds to high doses of opioids. Portenoy has stated that opioid responsiveness is partly a matter of dosage and that satisfactory outcomes can be obtained following dose escalation to an endpoint determined by either adequate analgesia or intolerable side effects. Benedetti et al suggest that postop neuropathic pair responds to opioid, opioid responsiveness of neuropathic pain is partly a matter of dosage and higher doses of opioids that are necessary to relieve neuropathic pain may be not a characteristic of neuropathic pain per se but a general feature related to the individual. A randomized double–blind active–placebo–controlled crossover trial suggested that fentanyl may relieve non–cancer neuropathic pain by its intrinsic analgesic effect. The indiscriminate prescribing of chronic opioids, seductive hypnotics and muscle relaxants, however, is without justification, especially if patients are not experiencing decreased pain and increased function.

Agents that may soon be available for the treatment of neuropathic pain include: 1) butyl–para–amino–benzoate (Butamen®), an ester local anesthetic, 2) bupivacaine microspheres, and 3) SNX–III, a selective calcium channel blocker. Nicotinic acetylcholine receptor agonists such as ABT–594, which may also prove efficacious, are in preliminary research stages. Animal studies have revealed the following as potential therapies in neuropathic pain 1) electroconvulsive treatment 2) intrathecal injection of chromaaffin cells 3) intrathecal injection of Nitric oxide synthase inhibitor L–N––G–nitro arginine methyl ester (L–NAME) 4) intrathecal neostigmine. A clinically available agent which is currently being investigated for the treatment of neuropathic pain is levodopa.

**Conclusion:**

Clearly, numerous pharmacological agents are available for the treatment of neuropathic pain. The definitive drug therapy has however remained elusive. Oftentimes triple drug therapy with tricyclic antidepressants, anti–convulsants and a systemic local anesthetic is necessary. Occasionally, there is the patient who requires chronic opioid therapy in conjunction with the above medications. When patients fail systemic treatments implantable systems, such as a spinal cord stimulator, or intrathecal morphine pumps are available. Recently, the spinal cord stimulator has been shown to attenuate the augmented dorsal horn release of excitatory amino acids via a GABAergic mechanism in rats. Rarely, surgical intervention is required.