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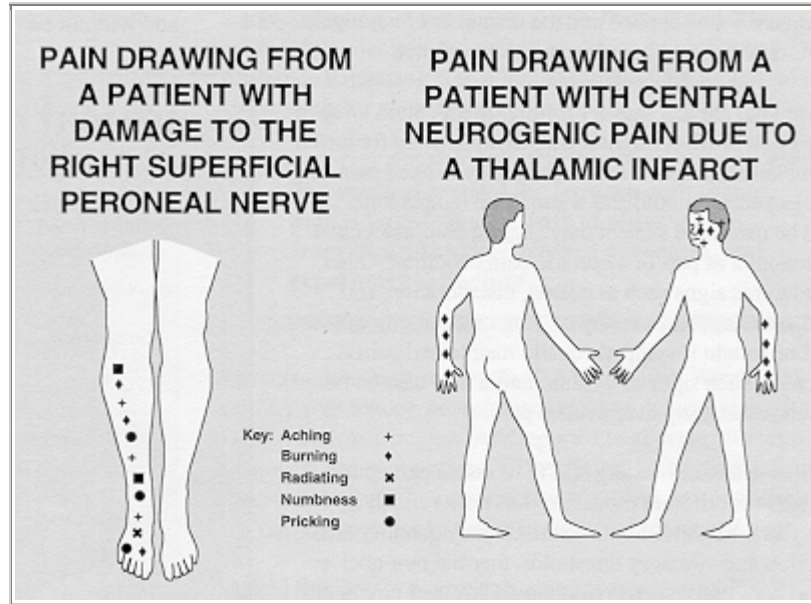
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## Neurogenic Pain: Diagnosis and Treatment

Pain that arises from the nervous system is termed "neurogenic." Peripheral neurogenic pain may follow transient pressure upon or stretching of a peripheral nerve or root, or reflect sustained damage to a nerve ("neuropathic pain") such as in polyneuropathy, entrapment neuropathy, or after herpes zoster.<sup>1</sup> Neurogenic pain may have a central origin such as stroke, multiple sclerosis, or trauma, especially of the spinal cord.

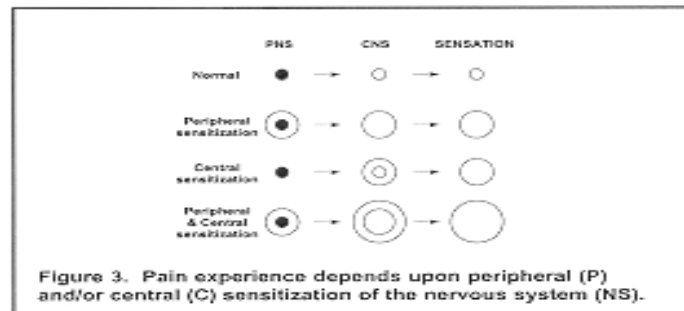
### Diagnosis

Correct diagnosis allows tailoring treatment to the pathophysiologic mechanisms that trigger and maintain the painful condition. Assessing the pain location, intensity, quality, time course, precipitating and relieving factors, as well as its impact on physical and psychosocial function is the first step in clinical analysis.<sup>2</sup> Diagnosis depends upon, first, the neuroanatomical distribution of the pain and, second, evidence of sensory dysfunction involving a peripheral nerve, plexus, nerve root or central pathway. If the affected nerve or pathway is mixed motor and sensory, then weakness, muscle atrophy, or reflex abnormalities may be additional clues to neural involvement. The diagnosis may be obvious but sometimes a thorough neurological examination is needed to uncover the neurogenic origin of the pain. A pain drawing made by the patient frequently gives a good indication of the neuroanatomic distribution and quality of the pain (Fig 1).



**Figure 1**

Impaired sensation is often evident during a careful examination. Sensory dysfunction may be manifested as hypo- and/or hyperesthesia for one or more modalities, increasing pain to normally painful stimuli (hyperalgesia) or pain due to normally nonpainful stimuli (allodynia) (Fig 2). Temporal and spatial sensory dysfunction are also common (Table 1).



**Figure 2.** Abnormal sensory function in neurogenic pain states can, regardless of modality, be described in terms of stimulus strength and sensation magnitude. (A) Hypoesthesia ("Hypo" thick line) consists of both increased perception threshold and reduced sensation magnitude at suprathreshold stimulus strengths. Occasionally, hypoesthesia occurs without an increase in stimulus detection threshold (thin line). (B) Elevated stimulus perception threshold, together with an increase in slope of the magnitude/stimulus relation is typical for the combination of hypo- and hyperesthesia often seen in neurogenic pain states. Evoked sensation hyperpathic syndrome (thick line) often has a paresthetic or dysesthetic character or is frankly painful instead of the normal sensation evoked by the applied stimulus. (C) Hyperesthesia can also occur separately with a steeper slope, and occasionally (thin line), with a lowered threshold. Adapted from Lindblom and Ochoa<sup>32</sup>

**Table 1. SENSORY ABNORMALITIES IN PATIENTS WITH NEUROGENIC PAIN**

Quantitative	Hypoesthesia Hyperesthesia	Hypoalgesia Hyperalgesia
Qualitative	Allodynia Paresthesia Dysesthesia	
Spatial	Dyslocalization Radiation	
Temporal	Abnormal latency Abnormal aftersensation Abnormal summation	

It is important to test all somatosensory modalities since dysfunction confined to a single modality may otherwise escape detection. Because tests of deep sensation (e.g., in subcutaneous tissue, muscle, and viscera) are lacking, one can only examine sensory function in a nerve or tract that has a cutaneous representation. If nerve damage is limited to deeper tissues, the second diagnostic criterion cannot be applied and the diagnosis of neurogenic pain remains tentative and based on indirect evidence.

Conventional clinical sensory testing uses a cotton swab or camel's-hair brush for light touch, figure writing for tactile discrimination, pinprick for mechanically evoked pain, and one object each for cold and warm. Skin temperature should be measured since it may suggest pain-associated dysautonomia as part of a specific pain condition. Other dysautonomic signs such as edema, discoloration, and altered sweating; and atrophy of skin, nails, or other tissue should be sought if sympathetically maintained pain is suspected.<sup>3</sup> Such signs of dysautonomia may also be found with sympathetically independent pain.

Quantitative sensory testing (QST) to assess perception thresholds for different modalities has been refined in recent years. Methods now exist to directly quantify tactile perception and vibratory thresholds, thermal non-nociceptive and nociceptive perception thresholds, and pinch- or pressure-pain thresholds.<sup>4</sup> When "bedside" testing is inconclusive, e.g., when any form of skin contact during sensory testing evokes pain, QST of different sensory modalities is mandatory to profile somatosensory function. Careful clinical examination to identify the spatial distribution of sensory abnormalities and other problems should always precede QST. Bedside clinical assessment guides the sites and methods of QST employed. Provocative maneuvers may be needed in cases of intermittent mechanical stress upon nerves or roots because sensory dysfunction may not be apparent at rest.

## **Treatment**

### **TENS**

Treatment for patients with peripheral neurogenic pain begins with transcutaneous electrical nerve stimulation (TENS).<sup>5</sup> When both high- and low-frequency stimulation techniques are tried, TENS will benefit some patients with peripheral neurogenic pain. In central neurogenic pain, TENS is less effective.<sup>6</sup> Occasionally TENS worsens pain. Reported side effects are limited to allergic reactions to the electrode gel and interference with cardiac pacemakers. Prior to TENS trial in a patient with a pacemaker, the cardiologist should be consulted.

## Drugs

The number of carefully designed treatment trials for neurogenic pain is low. The medical arsenal for treating neurogenic pain (Table 2) is based on a mixture of observations from clinical studies, clinical anecdotes, and experimental findings. Because there are no predictors for choice of medication, the current strategy is a "trial and error" procedure that yields clear improvement in only a minority of patients with central or peripheral neurogenic pain. Strategies for treating sympathetically maintained pain were described in an earlier *Pain: Clinical Updates*<sup>3</sup> and will not be repeated here. Neurosurgical ablation or stimulation techniques are also important therapeutically. Detailed discussion of these specialized methods will appear in a future issue of *Pain: Clinical Updates*.

Antidepressants	Amitriptyline Clomipramine Desipramine Imipramine Maprotiline Paroxetine
Anticonvulsants	Carbamazepine Phenytoin Valproate Clonazepam Baclofen
Antiarrhythmics	Mexiletine
Local anesthetics	Including topical agents
Topical	Capsaicin
Opioids	Oral Transdermal

Antidepressants are believed to potentiate the effect of biogenic amines in endogenous pain-relieving systems. The anticholinergic and antihistaminergic effects of antidepressants may also contribute to the analgesic effects of these drugs. Antidepressants in general, and amitriptyline in particular, provide analgesia in a

subgroup of patients with peripheral<sup>7-10</sup> and central<sup>11</sup> neurogenic pain states. In patients with painful diabetic neuropathy the selective serotonin uptake blocker fluoxetine was no more effective than placebo,<sup>10</sup> suggesting that antidepressants' efficacy for neurogenic pain depends mainly on noradrenergic uptake inhibition. Antidepressant trials in peripheral neurogenic pain have focused on postherpetic neuralgia<sup>7,9</sup> and painful diabetic polyneuropathy,<sup>8,10</sup> two conditions in which multiple pathophysiologic mechanisms may produce pain. Future trials should subdivide patient groups based on a thorough examination, perhaps using meticulous sensory analysis to search for predictors of successful treatment.

Anticonvulsants, particularly carbamazepine, were formerly the initial treatment in neurogenic pain (peripheral or central) if symptoms were paroxysmal and allodynia or hyperalgesia were present. The current view seems to be that in these conditions, trigeminal neuralgia excluded, amitriptyline should be the first choice.<sup>12</sup> For unclear reasons, pain relief during antidepressant therapy for postherpetic neuralgia seems not to be correlated with drug dosage or plasma concentration.<sup>9</sup> Leijon and Boivie,<sup>11</sup> however, found a correlation between plasma amitriptyline concentration and pain relief in patients with central post-stroke pain. In practice, treatment of neurogenic pain should be based on the balance of pain relief and side effects rather than plasma concentration of the drug and its metabolites. Such a balance is typically reached at a dosage of 75 to 150 mg of amitriptyline or maprotiline per day.

Spontaneous discharge of damaged peripheral or central neurons, or disinhibited, hyperexcitable central neurons may perpetuate certain neurogenic pain states.<sup>13,14</sup> In such cases and when antidepressant therapy fails or is poorly tolerated, drugs such as "membrane-stabilizing" antiepileptics, local anesthetics, and antiarrhythmics may reduce the excitability of neurons by interfering with initiation of the action potential. Controlled studies using these drugs are rare. Among the antiepileptic drugs<sup>15</sup> carbamazepine and, to some extent, phenytoin are the most commonly used in doses equivalent to those for antiepileptic treatment. Mexiletine, an oral antiarrhythmic lidocaine analogue, has shown promise in early studies for alleviating both peripheral<sup>16</sup> and central<sup>17</sup> neurogenic pain in a daily dose of about 10 mg/kg. The use of mexiletine stems from observations of analgesia in painful neuropathy during systemic lidocaine administration but controlled studies are needed to judge its value in neurogenic pain states. Even though patients with painful mononeuropathy seem to have signs of central dysfunction on examination, a peripheral block with local anesthetic often removes the pain<sup>18</sup>. Signs of central dysfunction found during examination (e.g., allodynia and dysesthesia) may, therefore, require input from the periphery to be maintained. The possibility that hyperexcitable central neurons have increased susceptibility to systemically absorbed local anesthetics cannot, of course, be excluded. Long-term pain relief for up to six days was achieved by Arner et al.<sup>18</sup> after single blocks in patients with painful mononeuropathies. The existence of possible long-term benefits of repeated blocks remains to be systematically explored. Benefits from systemically administered local anesthetics (e.g., intravenous lidocaine 1 to 5 mg/kg/hr) have also been reported in post-herpetic neuralgia,<sup>19</sup> painful diabetic neuropathy,<sup>20</sup> and central neurogenic pain.<sup>21</sup> As with other treatment modalities for neurogenic pain, predictors of favorable outcome using local anesthetics are not yet defined.

Topical application of local anesthetics (lidocaine and prilocaine in combination, EMLA) that penetrate the skin is a recent therapeutic alternative for neuropathic pain with localized hyperalgesia and allodynia. Uncontrolled studies on post-herpetic neuralgia<sup>22</sup> suggest that, in such cases, topical capsaicin (the active ingredient in hot peppers) may be indicated. The analgesic action of capsaicin is thought to be due to its ability to release substance P, causing activation and subsequent inhibition of small-diameter nociceptive fibers.

**The medical arsenal for treating neurogenic pain is based on a mixture of observations from clinical studies, clinical anecdotes, and experimental findings.**

Gamma-aminobutyric acid (GABA) is a widely distributed, primarily inhibitory, neurotransmitter. Drug interaction with GABA transmission has been reported to alleviate different neurogenic pain conditions.<sup>23</sup> The clinical impression, however, is that such drugs (e.g., clonazepam or baclofen) do not give substantial relief, except for baclofen treatment of trigeminal neuralgia.<sup>24</sup>

Opioid therapy for neurogenic pain is controversial.<sup>19,25,26</sup> Clinical evidence of relative opioid insensitivity of neurogenic pain is consistent with the experimental finding of a reduction of opioid receptors in the spinal cord dorsal horn after peripheral nerve damage.<sup>27</sup> Another recent hypothesis used to explain relative or total opioid insensitivity in chronic neurogenic pain is an increase in synthesis of the neuropeptide cholecystokinin (CCK) within the spinal cord as a result of peripheral nerve damage.<sup>28</sup> CCK exerts opioid antagonist effects and could, therefore, offset opioid analgesia. Although the long-term benefits of opioids for chronic neurogenic pain are not well established, some patients appear to respond well.<sup>26</sup> Therefore, at present, a logical clinical approach is to initiate and titrate opioid dosage according to individual needs.

Recently, the first report of intrathecal administration of an N-methyl-D-aspartate (NMDA) antagonist to a patient with neurogenic pain was published.<sup>29</sup> Pain was reduced but there were prominent psychiatric side effects. Ketamine, an anesthetic that also acts as an NMDA receptor blocker, has recently been found to decrease the pain of postherpetic neuralgia.<sup>30</sup> NMDA receptors mediate long-term excitatory effects of nociceptive transmission but these receptors also are present in areas of the CNS unrelated to pain or nociception. It is not known whether subpopulations of NMDA receptors are "pain-specific." If such subpopulations do exist, it may be possible to develop NMDA receptor antagonists that produce analgesia without intolerable side effects.

The novel neurotransmitter gas nitric oxide (NO) has recently been recognized as playing an important role in nociceptive processing in the spinal cord,<sup>31</sup> in part as a mediator of the cellular responses to NMDA receptor activation. Drugs to inhibit NO production are a natural goal for future research.

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## **Conclusion**

Current drug and nondrug therapies for patients with chronic neurogenic pain offer substantial pain relief to no more than half of those afflicted with such pain. Effective new drugs to treat neurogenic pain conditions are therefore desperately needed. In addition, placebo-controlled, double-blind studies with long-term follow-up are needed to conclusively judge the efficacy of current therapies.

On the bright side, knowledge of pathophysiologic mechanisms underlying neurogenic pain has grown exponentially during the last decade. This knowledge offers many possible approaches for pharmacological intervention (e.g., neurotransmitter antagonists given singly or with other drugs to decrease excitability at the membrane level or inhibit different steps of the nociceptive transmission process). Recent findings indicate that stimulation techniques and pharmacological treatments, alone or in combination, have therapeutic potential to normalize altered responsiveness of the CNS. Developing techniques to manipulate mechanisms of neural plasticity is a crucial task for future pain research.

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*Per Hansson, MD, PhD, DDS*

*Associate Professor, Neurogenic Pain Unit*

*Department of Rehabilitation Medicine*

*Karolinska Hospital/Institute*

*Stockholm, Sweden*

## **References**

1. Mohamed SA, Carr DB. *Pain Clin Update* 1994; 2(1):1–4.
2. Turk DC. *Pain Clin Update* 1993; 1(3):1–4.
3. Per E. *Pain Clin Updates* 1993; 1(4):14.
4. Hansson P, et al. *Pain Digest* 1993; 3:36–42.
5. Sjökind BH. *Pain Digest* 1993; 3:23–26.
6. Leijon G, et al. 1989; 187–191.
7. Watson GP, et al. *Neurology* 1982; 32:671–673.
8. Max MB, et al. *Neurology* 1987; 37:589–596.
9. Watson CP, et al. *Pain* 1992; 48:29–36.
10. Max MB, et al. *N Engl J Med* 1992; 326–1250–1256.
11. Leijon G, et al. *Pain* 1989; 36:27–36.
12. Max MB. *Pain* 1990; 42:131–133.
13. Lombard M-C, et al. *Pain* 1979; 6:163–174.
14. Wall PD, et al. *Pain* 1983, 17: 321–339.
15. Swerdlow M. *Pain Clinic* 1986, 1(1):9–19.
16. Degard A, et al. *Lancet* 1988; 1:9–11.
17. Awerbuch G. *J Neurosci* 1990; 55:129–133.
18. Arner S, et al. *Pain* 1990, 43:287–297.
19. Rowbotham MC, et al. *Neurology* 1991; 41:1024–1028.

20. Kastrup J, et al. *Pain* 1987; 28:69–75.
21. Edwards WT, et al. *Reg Anaesth* 1985;10:1–6.
22. Watson CPN, et al. *Pain* 1988; 33:333–340.
23. Swerdlow M. *Clin Neuropharmacol* 1984; 7(1):51–82.
24. Terrence CF, et al. *Eur Neurol* 1985; 24:380–385.
25. Arner S, et al. *Pain* 1988; 33:11–23.
26. Portenoy RK, et al. *Pain* 1990; 43:273–286.
27. Lombard M-C, et al. *Pain* 1989; 37:335–345.
28. Weisenfeld-Hallin Z, et al. *Proc Natl Acad Sci USA* 1990; 87:7105–7109.
29. Krisentensen, et al. *Pain* 1992; 51:249–253.
30. Eide PK, et al. *Pain* 1994; 58:347–354.
31. Meller ST, et al. *Pain* 1993; 52:127–136.
32. Lindblom U, Ochoa J. In: Asbury AK, et al. (Eds). *Diseases of the Nervous System*. WB Saunders 1992, pp 213–228.

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