Managing Neuropathic Pain

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"Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."

- International Association for the Study of Pain

Because of the inherent subjective nature of pain, and the fact that the word "pain" itself connotes multiple meanings, the International Association for the Study of Pain (IASP) has established a standardised definition of pain.

The definition makes several important points:

- Pain is an unpleasant emotional experience as well as an unpleasant sensory experience. This distinction between the sensory aspects of pain and its emotional (or affective) component has had a significant influence on both research and the treatment of chronic pain.
- Also emphasised by the IASP in defining pain is that pain is always subjective. If patients regard their experience as pain and if they report it in the same ways as pain caused by tissue damage, it should be accepted as pain.

IASP Task Force on Taxonomy. In: Merskey H, Bogduk N, eds. *Classification of Chronic Pain*. 2nd ed. Seattle, Wash: IASP Press; 1994:209-214.

Acute vs Chronic Pain

The causes of acute pain are often known, but the causes of chronic pain and its associated symptoms are not well understood.[1]

The pain experienced by patients with acute pain often can be alleviated. In general, the duration of acute pain is brief and has been well characterised.[1] The time course of chronic pain, however, is usually indeterminate, and patients with chronic pain are often refractory to treatment.[2]

One definition of chronic pain is pain that it has persisted beyond the time of normal healing; for research purposes, however, chronic pain is often defined as pain that has persisted at least 3 (sometimes 6) months.[3]

Because chronic pain can almost never be cured,[4] optimal treatment usually involves helping the patient restore function and supporting a patient's coping by utilising approaches that minimise pain, maximise QOL, improve sleep, and enable patients to return to work and perform their regular activities.[3,4]

[1] Galer BS, Dworkin RH. *A Clinical Guide to Neuropathic Pain*. Minneapolis, Minn: The McGraw-Hill Companies, Inc; 2000:7-8.
[2] Rowbotham MC. Chronic pain: from theory to practical management. *Neurology*. 1995;45(suppl 9):S5-S10.
[3] Portenoy RK, Kanner RM. Definition and assessment of pain. In: Portenoy RK, Kanner RM, eds. *Pain Management: Theory and Practice*. Philadelphia, Pa: FA Davis Company. 1996:6.

[4] Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. *Lancet*. 1999;353:1959-1964

Domains of Chronic Pain

Chronic pain has a wide range of negative effects, not only for the individual patient but for families and society as well.

Both physical and psychological aspects of a patient's life may be impacted, including the ability to work or perform activities of daily living, sleep patterns, emotional state (depression, anxiety, anger), and self-esteem.

Social, familial, marital, and/or sexual relations may be impaired, and patients may become socially isolated as they are no longer able to participate in their usual activities.

The disability and lost workdays associated with chronic pain impose significant direct as well as indirect healthcare costs for society as a whole. The economic impact of chronic pain is staggering. Back pain, migraines, and arthritis alone account for medical costs of $40 billion annually; the total annual cost of pain from all causes is estimated to be more than $100 billion. Pain is the cause of 25% of all sick days taken yearly.[5] (US Statistics)

A growing scientific understanding of pain mechanisms has led to the evolving concept of pain as a disease state in its own right, one that may require ongoing treatment.

However, do not expect analgesics to solve all these problems. A number of studies suggest that the best success in pain management relies on a multidisciplinary approach that includes patient education, medications, physical medicine, and psychological counseling. For example, when Becker et al compared the effect of multidisciplinary pain treatment (MPT) with that of treatment by a general practitioner after initial supervision by a pain specialist (GP group) in 189 patients with chronic, nonmalignant pain, they found that, after 6 months, the MPT group reported a statistically significant reduction in pain intensity (visual analog scale score, $P<.001$), improvement in psychological well-being (PGWB, $P<.001$), quality of sleep ($P<.05$), and physical functioning (Short Form-36–Physical Functioning, $P<.05$) compared with the GP group.[6]

Thus, a coordinated approach to pain management often provides the most efficient and cost-effective approach, which leads to patient empowerment (improved perception of personal control over pain) and the best clinical outcome.

Nociceptive vs Neuropathic Pain

Nociceptive, or inflammatory, pain is pain resulting from activity in neural pathways caused by potentially tissue-damaging stimuli.[7] Examples include postoperative pain, arthritis, mechanical low back pain, sickle cell crisis, and sports or exercise injuries.

Neuropathic pain is pain caused by a primary lesion or dysfunction in the peripheral and/or central nervous systems.[8] Examples of peripheral neuropathic pain syndromes include HIV sensory neuropathy, post herpetic neuralgia (PHN), and diabetic neuropathy. Examples of central neuropathic pain include central post-stroke pain, spinal cord injury pain, trigeminal neuralgia, and multiple sclerosis pain.

Chronic pain can be of mixed etiology with both nociceptive and neuropathic characteristics.

Descriptions of Neuropathic Pain

A variety of terms are used to describe neuropathic pain: numbness, tingling, burning, paroxysmal, paresthetic, lancinating, electric like, raw skin, shooting, deep, dull, and bonelike aching pain.

Additional terms that are often used to describe neuropathic pain include squeezing, jabbing, broken-glass, cramping, spasms, icy cold, and frostbite.

These terms are not perfectly sensitive or specific and are to be used only as a guide. Some patients with neuropathic pain will not use these

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[5] *U.S. News & World Report*. Washington, DC: U.S. News & World Report L.P.; March 17, 1997:55-57, 60-62, 65, 67.

[6] Becker N, Sjogren P, Bech P, Olsen AK, Eriksen J. Treatment outcome of chronic non-malignant pain patients managed in a Danish multidisciplinary pain centre compared to general practice: a randomized controlled trial. *Pain*. 2000;84:203-211.

[7] Portenoy RK, Kanner RM. Definition and Assessment of Pain. In: Portenoy RK, Kanner RM, eds. *Pain Management: Theory and Practice*. Philadelphia, Pa: FA Davis Company; 1996:4.

[8] Galer BS, Dworkin RH. *A Clinical Guide to Neuropathic Pain*. Minneapolis, Minn: The McGraw-Hill Companies Inc; 2000:8-9.

terms to describe their pain experience, and some patients who use these terms have non-neuropathic pain.

The primary signs and symptoms of neuropathic pain are allodynia (when all stimuli are painful) and hyperalgesia (when painful stimuli trigger more pain than expected).[9]

Physiology of Pain Perceptions

Pain that manifests in diverse diseases may operate through common mechanisms. No pain mechanism is an inevitable consequence of a particular disease process. A given pain mechanism could be responsible for many different symptoms. More than one mechanism can operate in a single patient, and these may change over time.

Transduction: Translation of physical stimuli into chemical processes. Painful stimuli cause ion channels in the membranes of thermal, mechanical, and chemical receptors located in the skin and tissues to open. Ions enter the receptor and depolarize it. If the change reaches a threshold, it will fire up the neuron.

Transmission: a wave of depolarization, or action potential, travels toward the spinal cord and up the ascending pathway. A-beta (light touch) fibers may become sensitized by CNS mechanisms to produce allodynia.

Modulation/Perception: the ascending pain pathway carries impulses from the nociceptor to the sensory cortex; thus the sensation of pain is perceived.

Interpretation: impulses are carried by 1st, 2nd, and 3rd order neurons. 1st order neurons carry impulses from the nociceptor to the spinal cord. 2nd order neurons carry impulses from the spinal cord to the thalamus while 3rd order neurons carry the impulse from the thalamus to the sensory cortex The main neurotransmitter is the excitatory amino acid glutamate.

Crossman AR, Neary D. *Neuroanatomy*, 2nd ed. Churchill Livingstone, 2000.

Galer B, Gammaitoni A, Alvarez N. 6. Immunology [XIV. Pain]. In: Dale DC, Federman DD, eds. *WebMD Scientific American® Medicine.* New York, NY:WebMD Corporation; 2003.

Guyton AC, Hall J. *Textbook of Medical Physiology,* 10th Ed. Saunders, 2000.

Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. *Lancet*. 1999;353:1959-1964.

Pathophysiology of Neuropathic Pain

Many mechanisms have been proposed for neuropathic pain, but it is unknown which mechanisms are most relevant in humans. In an individual patient, more than one mechanism is probably relevant. The ability to classify patients based on predominant pathophysiology may, hopefully, help target therapy.[10]

Excitotoxicity: nerve damage results in a barrage of nociceptive input released into the spinal cord that can damage inhibitory cells and result in a disinhibited pain system.[11]

Sodium channels: in damaged nerves, abnormal sodium channels may be produced that result in a hyper-excitable nerve.[12]

Ectopic discharge: damaged nerves produce ectopic, or abnormal, nerve impulses that may promote pain perceptions. [13]

Deafferentation: if the central nervous system (CNS) is deprived of normal nerve input, as in the case of amputation or plexus avulsion, pain may result. The classic picture is severe pain in an insensate (or absent) limb.[13]

Central sensitization: with repeated sensory input, the CNS may become hyper-responsive (sensitized) to peripheral input, a so-called facilitated state. This state is caused by long-term or permanent changes in the anatomy or physiology of the CNS produced by pain.[11-13]

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[9] Backonja M-M, Galer BS. Pain assessment and evaluation of patients who have neuropathic pain. *Neurol Clin*. 1998;16:775-789.

[10] Galer BS. Neuropathic pain of peripheral origin: advances in pharmacologic treatment. *Neurology*. 1995;45(suppl):S17-S25.

[11] Brookoff D. Chronic pain: 1. A new disease? *Hosp Pract*. July, 2000:45-52,59.

[12] Baron R. Peripheral neuropathic pain: from mechanisms to symptoms. *Clin J Pain*. 2000;16: S12-S20.

[13] Portenoy RK. Neuropathic pain. In: Portenoy RK, Kanner RM, eds: *Pain Management*: *Theory and Practice*. Philadelphia, Pa: FA Davis Company; 1996:94,97.

Multiple Pathophysiologies May Be Involved in Neuropathic Pain

Neuropathic pain may result from the concatenation of a number of mechanisms. Due to this multiplicity of mechanisms, it is unlikely that neuropathic pain corresponds to a unique entity. Each painful symptom may therefore *correspond* to a distinct mechanism and may only *respond* to a specific treatment.

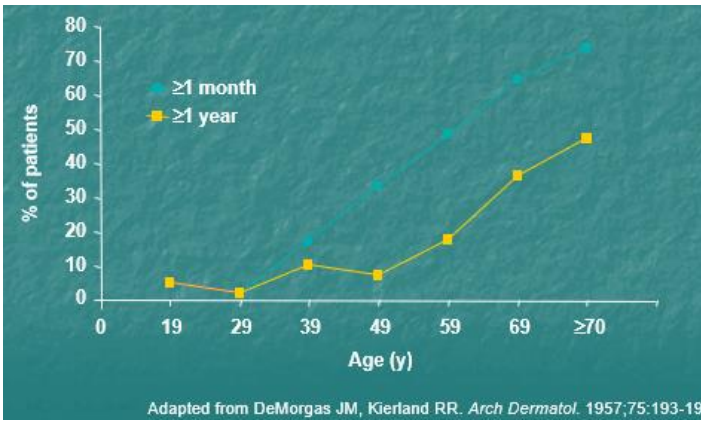
Spontaneous pain and paraesthesias associated with sodium channel activity, for example, may best respond to sodium channel blockers or antiepileptic agents. Increased transmission and reduced inhibition associated with hyperalgesia and allodynia may best respond to opioids or tricyclic antidepressants.

Sensitive and specific diagnostic tools are needed to reveal the particular pathological processes involved in the pain experienced by the individual patient. But accurate diagnosis of pain mechanisms will only occur if the mechanisms can be adequately targeted with appropriate therapies.

Attal N, Bouhassira D. Mechanisms of pain in peripheral neuropathy. *Acta Neurol Scand Suppl.* 1999;173:12-24.

Woolf CJ, Manion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. *Lancet.* 1999;353:1959-1964.

Percentages of Herpes Zoster Patients with Persistent Pain



These classic epidemiologic data show that the risk for persistent pain of 1 or more months' duration (upper line) or 1 or more years (lower line) increases with age in herpes zoster patients. One year after the onset of herpes zoster, only 4.2% of patients younger than 20 years were still experiencing pain, compared with 47% of patients older than 70 years.[14]

Although, as shown on the graph, comparatively few patients younger than 40 years report pain 1 month after rash healing, almost 50% of herpes zoster patients older than 70 years continue to experience pain 1 year or more after the onset of their zoster infection.[15]

Other risk factors associated with increased risk of PHN include greater severity of acute herpes zoster pain, greater herpes zoster rash severity/greater number of lesions, presence of a painful prodrome, and greater degree of sensory impairment in the affected dermatome.[2]

Additional data suggest that the risk of PHN may be slightly increased in patients with ophthalmic zoster. Although the data are inconsistent, some reports suggest that women have a slightly higher incidence of PHN than do men.[16]

Assessing the Patient in Pain

Assessment should include an evaluation of a patient's associated features and associated factors. The features include neurologic deficit and hyperphenomena, and among the associated factors are the psychosocial state (indicated by the patient's mood and level of emotional distress) and the impairment of functional activities, including activities of daily living, such as the ability to work or sleep.[18]

Rational treatment cannot proceed without detailed records of previous treatments, including dosages, duration of therapy, side effects, and reason for stopping treatment.[1]

[14] DeMorgas JM, Kierland RR. The outcome of patients with herpes zoster. *Arch Dermatol*. 1957;75:193-196.
[15] Galer BS, Dworkin RH. *A Clinical Guide to Neuropathic Pain*. Minneapolis, Minn: The McGraw-Hill Companies, Inc; 2000:87-91.

[16] Kost RG, Straus SE. Postherpetic neuralgia–pathogenesis, treatment, and prevention. *N Engl J Med*. 1996;335:32-42.

Aims of Clinical Assessment

A crucial first step in diagnosing and treating pain is to acknowledge to patients that they are experiencing pain and that the pain is real.

Some patients with neuropathic pain will have an underlying disorder that can be cured or improved with disease-specific therapy, eg, B_{12} deficiency neuropathy or an entrapment neuropathy. If the diagnosis is missed, so is the opportunity to help the patient.[17]

All patients suspected of having neuropathic pain should be questioned about their pain history and receive a pain-specific sensory examination, a musculoskeletal and myofacial evaluation, and a basic psychologic assessment.

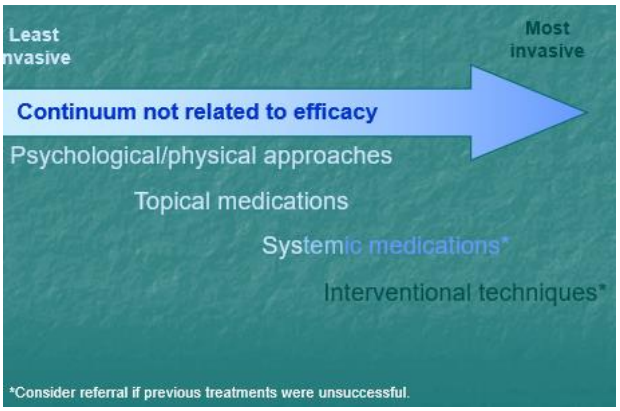
A patient's functional status can be assessed by evaluating their ability to perform the activities of daily living as well as their mood, ability to sleep, and coping skills.

Psychosocial factors, such as anxiety, depression, posttraumatic stress disorder, substance abuse, or work issues, may complicate treatment responses, and may require specific intervention.

Obtaining a specific pain diagnosis is important because it enables physicians to formulate a more specific and targeted treatment plan.

The pain assessment should help the physician decide if multidisciplinary intervention is needed from a pain medicine specialist, a psychologist, psychiatrist, and vocational counselor.[18]

Pain Treatment Continuum



The above image lists the various treatments for neuropathic pain in order of invasiveness.[19] However, the efficacy of treatment does not necessarily match its invasiveness. For some patients, behavioral or physical therapy or a topical medication can be at least as effective as an interventional technique.[22,20]

While there are many treatment options and combinations for neuropathic pain, we will focus on those meeting three important criteria:

1) efficacy—demonstrated in controlled clinical trials;

2) safety—demonstrated in controlled clinical trials and subsequent clinical experience;

3) favorable tolerability profiles (ie, side effects, drug/drug interactions).

Psychological/physical approaches to pain management include relaxation therapy and physical exercise programs.

Topical medications consist of the lidocaine patch 5%, capsaicin, and a variety of custom-compounded topical agents of unknown effectiveness.[21,22]

Oral medications include anticonvulsants, tricyclic antidepressants (TCAs), opioids, and miscellaneous agents (eg, mexiletine, baclofen).[22,25]

The two types of injections are nerve blocks and local infiltrations that are usually administered with local anesthetics and/or steroids.[23]

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[17] Katz N. Neuropathic pain in cancer and AIDS. *Clin J Pain*. 2000;16(suppl 2):S41-S48.
[18] Backonja M-M, Galer BS. Pain assessment and evaluation of patients who have neuropathic pain. *Neurol Clin*. 1998;16:775-789.
[19] Mackin GA. *J Hand Ther*. 1997;10:96-109.
[20] Leland JY. *Geriatrics*. 1999;54:23-37.
[21] Katz N. *Clin J Pain*. 2000;16:S41-S48.
[22] Belgrade MJ. *Postgrad Med*. 1999;106:127-148.
[23] Galer BS et al. *A Clinical Guide to Neuropathic Pain*. 2000:97.

The interventional techniques that require referral to a specialist are spinal cord stimulation, spinal analgesia, brain stimulation, and various neurosurgical procedures such as dorsal root entry zone lesions.[23,24]

Nonpharmacologic Options

Non-pharmacologic strategies may be useful in easing pain and improving function, especially if used adjunctively with pharmacologic remedies. However, nonpharmacologic strategies are rarely sufficient to replace pharmacotherapies, especially in the case of chronic neuropathic pain.[25]

A number of trials have demonstrated that transcutaneous electrical nerve stimulation has efficacy in ameliorating chronic neuropathic pain. However, the apparatus may be difficult for some patients to operate and the treatment itself is time-consuming.[26]

Pharmacologic Options

When selecting a pharmacologic treatment regimen, consideration should also be given to safety and tolerability factors such as side-effect profile and potential for drug interactions. Controlled clinical trials and clinical experience document that the lidocaine patch, because of its non-systemic mechanism of action, has the least potential for adverse side effects or drug interactions. Among systemic agents, gabapentin, which has no significant side effects, has demonstrated favorable safety and tolerability. Based on these factors, the lidocaine patch and gabapentin are often selected as initial treatments for neuropathic pain.[27,28,29,30,31,32]

Nortriptyline, desipramine, tramadol, and controlled-release oxycodone also have demonstrated safety and tolerability profiles which are more favorable than those of earlier agents much as amitriptyline, phenytoin, carbamazepine, and others.[30,31,33,34,35,36,37,38,39,40]

Licensed Treatments for Neuropathic Pain

Only five medications, pregabalin, duloxetine, lidocaine patch 5%, gabapentin, and carbamazepine, have been approved for the treatment of neuropathic pain—specifically, for treatment of diabetic peripheral neuropathy (DPN), postherpetic neuralgia (PHN), and trigeminal neuralgia.

Pharmacologic Agents Affect Pain Differently

Available drug treatments for chronic pain currently include simple analgesics such as pracetamol, nonsteroidal anti-inflammatory drugs, traditional opioid drugs, and adjuvant agents (eg, antidepressants, anticonvulsants). Typically, the choice of a drug is made by balancing the indications for treatment, the clinical efficacy of the drug, and its toxicity. An understanding of the mechanism of action of these drugs helps to establish their role in therapy.

Better understanding of the pathophysiology of acute and chronic pain has led to numerous advances in pharmacologic management of painful disorders, including low back pain, migraine headache, fibromyalgia, post-herpetic neuralgia, osteoarthritis, rheumatoid arthritis, and cancer-related neuropathic pain.

Opioids mimic the actions of endogenous opioid peptides by interacting with mu, delta, or kappa opioid receptors. Their actions are mainly inhibitory.

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[24] Gonzales GR. *Neurology*. 1995:45(suppl 9):S11-S16.
[25] Ferrell B, Herr K, Epplin J, et al. The management of persistent pain in older persons. *Programs and Abstracts of the American Geriatric Society 2002 Annual Scientific Meeting.* May 8–12, 2002; Washington, DC.
[26] Kuman D, Marshall HJ. Diabetic peripheral neuropathy: amelioration of pain withtranscutaneous electrostimulation. *Diabetes Care.* 1997;20:1702-1705.
[27] Backonja M et al. *JAMA*. 1998;280:1831-1836.
[28] Rowbotham M et al. *JAMA*. 1998;280:1837-1842.
[29] Carter GT et al. *Phys Med Rehabil Clin N Am.* 2001;12:447-459.
[30] Rowbotham MC et al. *Pain*. 1996;65:39-44.
[31] Galer BS et al. *Clin J Pain.* 2002;18:297-301.
[32] Galer BS et al. *Pain*. 1999;80:533-538.
[33] Rice AS et al. *Prostaglandins Leukot Essent Fatty Acids*. 2002;66:243-256.
[34] Gorson DM. *Diabetes Care*. 1998; 21:2190-2191.
[35] Max MB et al. *N Engl J Med*. 1992;326:1250-1256.
[36] Watson CPN et al. *Neurology*. 1998;51:1166-1171.
[37] Watson CP. *Clin J Pain.* 2000;16(suppl 2):S49-S55.
[38] Watson CP et al. *Neurology*. 1998;50:1837-1841.
[39] Harati Y et al. *Neurology*. 1998;50:1842-1846.
[40] Sindrup SH et al. *Pain.* 1999;83:389-400.

Inhibition of prostaglandin synthesis by cyclooxygenase is the principal mode of the analgesic and anti-inflammatory actions of NSAIDs. The widespread inhibition of cyclooxygenase is responsible for many of the adverse effects of these drugs. NSAIDs also reduce prostaglandin production within the CNS. This is the main action of paracetamol.

Argoff CE. Pharmacologic management of chronic pain. *J Am Osteopath Assoc.* 2002;102(suppl 3):S21-S27.

Aronson MD. Nonsteroidal anti-inflammatory drugs, traditional opioids, and tramadol: contrasting therapies for the treatment of chronic pain. *Clin Ther.* 1997;19:420-32; discussion 367-8.

Bovill JG. Mechanisms of actions of opioids and non-steroidal anti-inflammatory drugs. *Eur J Anaesthesiol Suppl*.1997;15:9-15.

Topical v Transdermal Systems

Topical treatment is not the same as transdermal treatment. Topical treatment means the drug stays and acts primarily locally, with minimal systemic absorption and effects. Transdermal treatment attempts to have systemic effects by delivering the drug through the skin instead of orally, intravenously, or by other means.

Because it is a topical agent, the lidocaine patch 5% achieves insignificant serum levels, even with chronic use. This enhances safety and makes drug interactions unlikely.[41] Clinical trials have shown no statistical difference between lidocaine patch 5% and placebo patch with regard to side effects.[42] The most common adverse event reported with the topical lidocaine patch 5% is transient minor local irritation of the skin.[43] It is applied directly to the affected area. The patch can be trimmed to cover a small area. However, up to three patches may be applied to intact skin for up to 12 hours within a 24-hour period.[44] This patch is indicated for treatment of PHN.[55]

Transdermal systems need to be applied to non-irritated skin. They deliver medication systemically, which means a slower onset of action. These are primarily opioi analgesics. Patients are advised to use short-acting analgesics until analgesic efficacy with the patch is achieved.

Because serum levels of the drug increase correlatively with duration of transdermal patch wear-time, side effects can be significant and problematic. Nausea, mental clouding, and skin irritation are commonly reported. More serious side effects include serious or life-threatening hypoventilation and bradycardia. Drug-drug interactions may also be a problem, especially concomitant use of the transdermal opioid patch and central nervous system (CNS) depressants (eg, benzodiazepines).[445]

Anticonvulsant Drugs for Neuropathic Pain Disorders

Anticonvulsant medications have been used in the treatment of neuropathic pain for many years without approval (except for carbamazepine's indication for trigeminal neuralgia). Pregabalin has approval for neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia. Many controlled trials have been conducted examining the efficacy of anticonvulsant drugs in the treatment of various neuropathic pain syndromes.[46,47,48,49,50,51,52]

The studies of carbamazepine and phenytoin conducted in the 1960s and 1970s do not meet today's standards of methodological rigor.[53] The phenytoin studies have produced both successful and unsuccessful results.[54]

[41] Argoff CE. New analgesics for neuropathic pain: the lidocaine patch. *Clin J Pain*. 2000;16(2 suppl):S62- S66.

[42] Galer BS, Rowbotham MC, Perander J, Friedman E. Topical lidocaine patch relieves postherpetic neuralgia more effectively than a vehicle topical patch: results of an enriched enrollment study. *Pain*. 1999;80:533-538.

[43] Galer BS, Dworkin RH. *A Clinical Guide to Neuropathic Pain.* Minneapolis, Minn: McGraw-Hill Companies Inc; 2000:61-64.

[44] Lidoderm (lidocaine patch 5%) [package insert].

[45] Duragesic [package insert]. Titusville, NJ: Janssen Pharmaceutica; 1999.

[46] Rowbotham M et al. *JAMA*. 1998;280:1837-1842.

[47] Eisenberg E et al. *Neurology.* 2001;57:505-509.

[48] Simpson DM et al. *Neurology*. 2000;54:2115-2119.

[49] Campbell FG et al. *J Neurol Neurosurg Psychiatry*. 1966;29:265-267.

[5050] Zakrzewska JM et al. *Pain*. 1997;73:223-230.

[51] Zakrzewska JM et al. *J Neurol Neurosurg Psychiatry*. 1989;52:472-476.

[52] Vestergaard K et al. *Neurology*. 2001;56:184-190.

[53] Rull J et al. *Diabetologia*. 1969;5:215-218.

[54] Chadda VS et al. *J Assoc Physicians India*. 1978;26:403-406.

The two studies of gabapentin are among the largest clinical trials of the treatment of neuropathic pain ever conducted.[70,71,55]

First-generation anticonvulsant drugs, which include carbamazepine and phenytoin, sometimes provoke serious side effects and drug-drug interactions that do not occur with second-generation anticonvulsants.[56]

Gabapentin in Neuropathic Pain Disorders

Gabapentin is an anticonvulsant which has approval for the treatment of PHN, but not for other neuropathic pain syndromes.[57]

Its mechanism of action has not been completely identified. It appears to interact with calcium channels.

Gabapentin has limited intestinal absorption and is usually well tolerated. Among the more common adverse events associated with its use are dizziness and sedation. It has rare serious adverse effects.

No clinically significant drug-drug interactions are known.

Plasma clearance decreases in older patients and in patients with impaired renal function.[58]

For pain, the usual dosage range is up to 3,600 mg/day (tid-qid).[74]

Antidepressants

Tricyclic antidepressants (TCAs) act in part by inhibiting the reuptake of norepinephrine and serotonin into presynaptic neurons. They have been used to relieve neuropathic pain, although this indication has not been approved.

However, many controlled clinical trials and meta-analyses have demonstrated that TCAs (eg, imipramine, amitriptyline, desipramine, nortriptyline, clomipramine) can significantly reduce the pain of diabetic neuropathy and PHN.[59,260,361,462]

Some, but not all, selective serotonin reuptake inhibitors (SSRIs) have also been shown to be effective for neuropathic pain. Paroxetine and citalopram have shown benefit for diabetic neuropathy,[76,77] while fluoxetine has proved to be no more effective than placebo.[78]

Some patients who receive antidepressants for neuropathic pain may experience improvement in insomnia, anxiety, and depression.[79,63] Onset of analgesia with antidepressants generally occurs before the onset of the antidepressant effect.

Adverse effects commonly reported with TCAs are anticholinergic effects. These include blurred vision, cognitive changes (such as concentration, memory loss, and confusion), constipation, dry mouth, orthostatic hypotension, sedation, tachycardia, and urinary retention. All TCAs are reported to cause these adverse events in varying degrees of frequency and severity.[64,65]

Desipramine offers the fewest adverse effects. Nortriptyline, imipramine, doxepin, and amitriptyline the most.[85,66]

Because of the potential for adverse events and outcomes, amitriptyline should not be prescribed for people older than 65 years. Desipramine would be more appropriate for this population. Of all the drugs that are inappropriate for the elderly,

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[55] Backonja M et al. *JAMA*. 1998;280:1831-1836.
[56] Ross EL. *Neurology.* 2000;55:S41-S46.
[57] Backonja M-M. Anticonvulsants (antineuropathics) for neuropathic pain syndromes. *Clin J Pain*. 2000;16:S67-S72.
[58] Neurontin (gabapentin) [package insert]. Morris Plains, NJ: Parke-Davis; 1999.
[59] Sindrup SH et al. *Pain*. 1990;42:135-144.
[60] Sindrup SH et al. *Clin Pharmacol Ther*. 1992;52: 547-552.
[61] Max MB et al. *N Engl J Med*. 1992;326:1250-1256.
[62] Galer BS et al. *A Clinical Guide to Neuropathic Pain*. 2000:71-72,93.
[63] Pappagallo M. *Rheum Dis Clin N Am*. 1999;25:193-213.
[64] Rowbotham MC, Petersen KL, Davies PS, et al. Recent developments in the treatment of neuropathic pain. *Proceedings of the 9th World Congress on Pain*. Seattle, Wash: IASP Press; 2000:833-855.
[65] Mackin GA. Medical and pharmacologic management of upper extremity neuropathic pain syndromes. *J Hand Ther*. 1997;10:96-109.
[66] Tunali D, Jefferson JW, Greist JH. *Depression and Antidepressants: A Guide*. Madison, Wis: Information Centers, Madison Institute of Medicine; 1999.

amitriptyline is one of most frequently prescribed.[67]

Because the TCAs appear to be almost equally efficacious, a rational approach for clinical practice is to start with the agents with the fewest adverse effects, unless a specific "side effect," such as nighttime sedation, is desired.

Duloxetine is a newer antidepressant that has approval for the treatment of neuropathic pain secondary to diabetes. It has a more favorable side-effect profile and similar efficacy to TCA.

Principles of Opioid Therapy for Neuropathic Pain

Opioid therapy entails a number of risks for patients, but these potential problems can be prevented or circumvented.

Titration of opioid analgesics should be based on optimizing therapeutic efficacy while minimizing side effects. Regimens of fixed doses are generally preferred over prn regimens.[68]

Documentation is critical and should include the initial evaluation, substance abuse history, psychosocial issues, pain/pain relief, side effects, functional outcomes, and continuing monitoring. Regular discussions with family members about the patient's condition and use of opioids can improve the accuracy of monitoring.[88]

Most opioid side effects can be controlled with appropriate specific management (eg, prophylactic bowel regimen, use of stimulants).[69]

Patients on opioids or those who appear to require them also have significant psychosocial rehabilitative issues and are generally best referred to a multidisciplinary center with experience managing chronic pain with opioids.[88]

Addiction is referred to by many as psychological dependence.

The Issue of Aberrant Drug-Taking Behaviors

Before considering initiation of opioid treatment, it is important for the physician, patient, and family to understand the distinction between physical dependence, tolerance, and addiction.

Physical dependence is a pharmacologic effect characterized by the development of a withdrawal syndrome when an opioid drug is discontinued, when the dose is substantially reduced or if an antagonist is administered. Dependence occurs in almost all patients on opioids, and does not connote addiction.[70]

Tolerance means that a greater amount of drug is needed over time to maintain a therapeutic effect. The number of patients who develop clinically relevant tolerance is unknown. Tolerance may also occur to side effects, and thus may be beneficial. Some patients who develop tolerance can have their pain managed by judicious dose increases;[71] others who develop inexorable tolerance cannot have their pain managed by opioids. There is no evidence to support a role for analgesic tolerance in the development of drug addiction. Addiction is, however, often (though not always) associated with tolerance.

Addiction is a psychiatric disorder consisting of continued, compulsive use of the substance despite harm.[91] *The Diagnostic and Statistical Manual of Mental Disorders* provides nine categories of opioid use or opioid-induced disorders, including diagnostic criteria for opioid dependence or opioid abuse.[72]

True addiction (patient loss of control) may become obvious only when the physician stops prescribing the medicine. In a study reviewing the available data, it was found that prevalence estimates for addiction in patients with chronic pain ranged from 3% to 19%.[473]

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Interventional Treatments for Neuropathic Pain

Interventional treatments for neuropathic pain include neural blockade, neurolytic techniques, and stimulatory techniques.

Neural blockade includes sympathetic blocks for complex regional pain syndrome type I (CRPS-I), which occurs without a definable nerve lesion and is also called reflex sympathetic dystrophy, and complex regional pain syndrome type II (CRPS-II), which occurs when a definable nerve lesion is present; both syndromes are also known as causalgia.[74,75]

Neurolytic techniques are primarily employed for pain caused by cancer.[76]

Pumps and stimulators are the main interventional techniques in routine clinical use.[96] Stimulatory techniques encompass spinal cord and peripheral nerve stimulation.[477] The main advantage of spinal cord stimulation is that it is a nonpharmacologic intervention.[78]

Advances in Treatment for Neuropathic Pain

There are a number of potential new treatments for neuropathic pain in clinical trials and open-label studies. Several of these emerging treatments are:

- Botulinum toxin: low back pain
- Lidocaine patch 5%: low back pain, osteoarthritis, diabetic and HIV-related neuropathy, with gabapentin
- Levetiracetam: neuropathic pain and migraine
- Oxcarbazepine: neuropathic pain; diabetic neuropathy
- Expanded uses of existing agents into non-licensed indications

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Summary

- Most patients can obtain clinically meaningful relief with appropriate treatment.
- Given the multiple mechanisms of neuropathic pain, polypharmacy may be required for patients who do not respond adequately to treatment with a single agent.
- Drugs should be titrated aggressively either to the point where significant pain relief is achieved or intolerable side effects occur.
- New treatments for neuropathic pain that target specific pathways may help address the underlying mechanisms involved in pain.
- Treatment should balance efficacy, safety, and tolerability, and progress from the least to the most invasive treatments. More invasive treatments are not necessarily more effective than less invasive ones. The goals of treatment should include not only reducing pain as much as possible but also improving the patient's QOL.[79]
- Patients with inadequate pain relief may benefit from referral to multidisciplinary pain treatment centers.[80]

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