Neuropathic pain

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Neuropathic pain is a distressing, poorly understood and under-treated condition. In this review we seek to examine the definition and classification of neuropathic pain, summarize clinically important underlying mechanisms, outline current management strategies and look at future directions for research and therapy.

Neuropathic pain is defined by the International Association for the Study of Pain (IASP) as:

'Pain initiated or caused by a primary lesion or dysfunction in the nervous system' (Merskey and Bogduk, 1994).

This implies that conditions in which pain results from stimulation of nociceptors (specialized pain receptors) are excluded. It is more difficult to decide what is included. For example, reflex sympathetic dystrophy, now known as complex regional pain syndrome type 2, is conventionally classified as a form of neuropathic pain but this can be questioned (Ochoa, 1999). Often it is impossible to verify a neurological lesion in patients and what constitutes 'dysfunction' is open to interpretation. More knowledge of pain pathophysiology is required to clarify the definition.

Neuropathic pain is pathological

Acute pain is part of our normal homeostatic physiology. Initiated by stimulation of nociceptors, it alerts us to real or potential tissue damage. We then undergo behavioural and physiological changes designed to protect the injured body part and promote healing.

Neuropathic pain in contrast is a pathological entity — the pain and suffering are the result of ongoing nervous system dysfunction that serves no apparent biological purpose.

Prevalence of neuropathic pain

The prevalence of neuropathic pain is unknown. Extrapolating from numbers of patients seen in hospital clinics, Bowsher (1991) calculated the prevalence of 'neurogenic pain' to be 1% in the British population. This is likely to be an underestimate. Many patients with chronic pain are never referred to hospital clinics and others stop attending when they or their doctors perceive no therapeutic benefit is being gained. Community-based surveys of chronic pain invariably report much higher prevalence than hospital-based studies. The prevalence of neuropathic pain is also likely to increase with ageing of the population.

Symptoms of neuropathic pain

In many situations, neuropathic pain and nociceptive pain co-exist. A clear understanding and separation of these two entities is important when formulating a rational treatment plan. This

TABLE 1.
Descriptions of neuropathic pain

Superficial sensations	Burning
	Cutting
	Stabbing
	Electric shock
Deep sensations	Aching
	Cramping
	Throbbing
	Crushing
Others	Rawness
	Tightness
	Pins and needles
Pattern of pain	Spontaneous (non-evoked)
	Precipitated by a stimulus (evoked)
Periodicity of pain	Continuous
	Intermittent
	Combined

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can only be achieved by careful assessment. Individual patients report their pain in a variety of ways and a common system is necessary to rationalize their symptoms. *Table 1* lists some descriptors of neuropathic pain and a method of assessing patients' symptoms. A combination of different neuropathic pain sensations is often present. For example, most patients with chronic painful diabetic neuropathy describe background constant heavy ache with spontaneous and evoked sharp burning pain.

Signs to look for with neuropathic pain

Neuropathic pain is usually accompanied by an alteration in sensory function. Signs to look for are listed in *Table 2*. Several of these signs may occur in the same patient concurrently or over time.

Causes of neuropathic pain

Any process that damages the sensory pathways can cause neuropathic pain (see *Table 3*).

Classification of neuropathic pain

Neuropathic pain has been historically classified according to the agent of insult and anatomical distribution. This method of classification was confirmed by the IASP task-force on taxonomy (Merskey and Bogduk, 1994).

Table 4 gives an example of the current taxonomy. This method of classification ignores the mechanism(s) underlying neuropathic pain. A good example of this is postherpetic neural-

TABLE 2.
Signs associated with neuropathic pain

Positive sensory signs	Static allodynia	Pain resulting from a static stimulus that would not normally cause pain (e.g. light pressure)
	Dynamic allodynia	Pain resulting from a dynamic stimulus that would not normally cause pain (e.g. stroking with cotton wool)
	Thermal hyperaesthesia	Non-nociceptive warm or cold stimulus perceived as painful
	Hyperalgesia	An increased response to a stimulus which is normally painful
	Hyperaesthesia	Increased sensitivity to stimulation (with or without pain)
	Hyperpathia	An increased painful response to a stimulus. This can coexist with an increased threshold (hypoaesthesia). A stimulus, for example light touch is not initially felt. Then with increased stimulus a threshold is overcome and a severe, often explosive, pain occurs that remains after cessation of the stimulus ('afterpain')
	Dysaesthesia	An abnormal and unpleasant sensation rather than true pain. It may be spontaneous or evoked
Positive motor signs	Involuntary movements	Dystonia, tremor, athetosis associated with pain
Negative signs	Hypoaesthesia	Decreased sensitivity to stimulation (of any modality)
	Associated trophic changes	Altered texture of skin and appendages e.g. thickened nails, loss of hair
	Associated motor signs	Muscle weakness and wasting in absence of damage to motor nerves. Can be impossible to distinguish from changes secondary to disuse

TABLE 3.
Causes of neuropathic pain

Trauma	Brachial plexus avulsion
	Causalgia
	Phantom pains
	Post-thoracotomy intercostal neuralgia
Nerve compression	Lumbosacral and cervical radiculopathies
	Thoracic outlet syndrome
	Syndromes of notalgia, cheiralgia and meralgia paraesthetica
Infection	Herpes simplex virus (postherpetic neuralgia)
	Human immunodeficiency virus
	Lightning pains of tertiary syphilis
Metabolic	Diabetes (plexopathy, mononeuropathies and peripheral neuropathies)
	Amyloidosis
	Vitamin deficiencies
	Pernicious anaemia
	Strachan's disease
Inflammatory	Systemic lupus erythematous
	Rheumatoid arthritis
	Polyarteritis nodosa
	Sarcoidosis
	Brachial neuritis
	Multiple sclerosis
Neoplastic	Direct infiltration into nerves, plexuses, nerve roots, spinal cord
Paraneoplastic	Painful peripheral neuropathies
Toxins and drugs	Alcohol
	Thallium
	Arsenic
	Vincristine
	Cisplatinum
	Taxol
	Amiodarone
	Isoniazid
Vascular	Post-stroke 'central pain'
	Some cases of trigeminal neuralgia
Genetic	Fabry's disease
	Amyloidosis

gia. Therapeutic trials have regarded postherpetic neuralgia patients as a single population. In reality, there are at least three sub-groups clearly identifiable according to their signs and symptoms (Fields et al, 1998). These types are represented in *Figure 1*. Therefore, neuropathic pain of a single aetiology may have different pathophysiological mechanisms. Conversely, neuropathic pain syndromes classified under different aetiologies may share common mechanisms. This would explain why the various traditional diagnostic entities of neuropathic pain respond similarly to therapies prescribed (see below).

Should we classify neuropathic pain in a different way? Woolf and Decosterd (1999) have suggested replacing the anatomical/aetiological classification with a new classification system based on mechanisms of neuropathic pain. It would be unwise to completely abandon the old system for several reasons. First, some aetiological causes of neuropathic pain demand different strategies. To ignore diabetes as the cause of painful peripheral neuropathy would be disastrous when tight glycaemic control is the proven way to retard disease progression (Parry, 1999). Second, our understanding of neuropathic pain mechanisms is largely derived from animal models and is far from complete. Third, an agreed uniform method of assessing patients to identify underlying pain mechanisms does not exist.

Retaining the traditional classification with the addition of a presumed mechanism of pain represents the best compromise. For example, a patient can be classified as having postherpetic neuralgia, predominantly deafferented non-allodynic type. The practical relevance of this is to choose centrally-acting drugs ahead of topical treatment for such a patient.

TABLE 4.
Classification of neuropathic pain

Agent of insult	Postherpetic neuralgia	
	Diabetic neuropathy	
	Human immunodeficiency virus-related neuropathy	
	Lightning pains of syphilis	
Anatomical distribution	Central	Central post-stroke pain
		Thalamic syndrome
		Syringomyelia
	Peripheral	Peripheral neuropathy
		Morton's metatarsalgia
		Meralgia paraesthetica
		Neuralgic amyotrophy

MECHANISMS OF NEUROPATHIC PAIN

Recent advances reveal a bewildering array of possible mechanisms in neuropathic pain (see *Figure 2*). Some of these with possible therapeutic potential are outlined in *Table 5*. Reviews by Besson (1999), Eglen et al (1999), Ramer et al (1999) and Yaksh (1999) give more detail.

THERAPY FOR NEUROPATHIC PAIN

The complexity and difficulty of treating neuropathic pain is reflected by the numerous drugs that are employed. Numbers needed to treat (NNT) has been introduced as a method to compare drug efficacy. NNT is the number of patients needed to treat with a certain drug to obtain one patient with 50% or more pain relief. An allowance is made for the placebo effect (see McQuay and Moore (1998) for a review). NNT values are calculated from meta-analysis of trials that invariably have some flaws. The NNT for different drugs cannot be

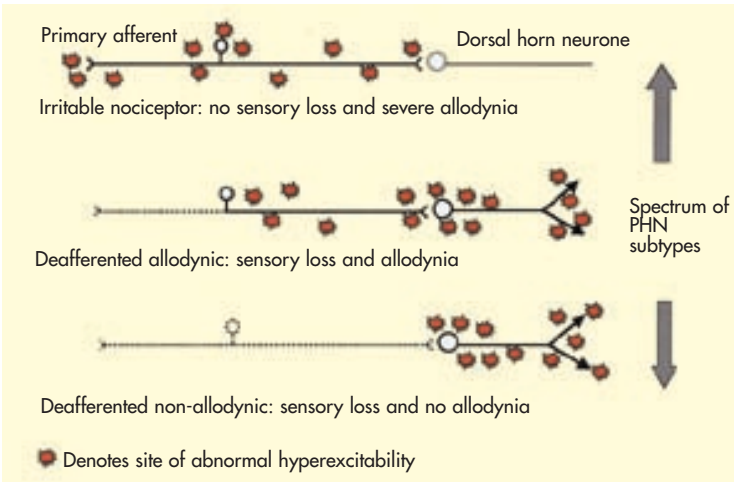

Figure 1. Different subtypes of postherpetic neuralgia (PHN).

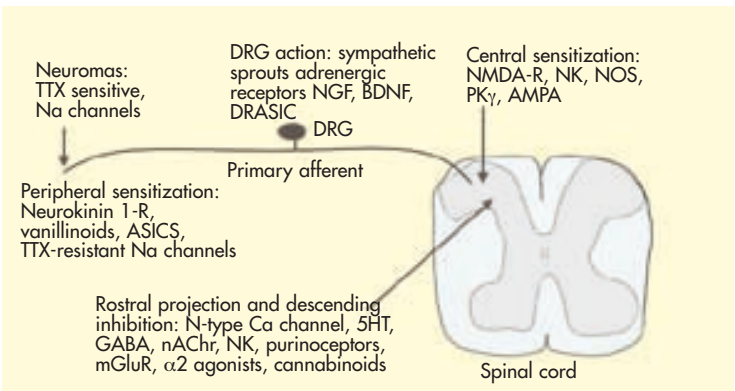

Figure 2. Mechanism and possible intervention sites in neuropathic pain.

used as a direct comparison for assessing efficacy as the study population in each trial is different. NNTs should be regarded as a best estimate.

Drugs: traditional primary analgesics are relatively ineffective

Paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) are relatively ineffective in pure neuropathic pain, although they are indicated in mixed pain states such as in cancer. There is some evidence that opioids are effective in some cases of neuropathic pain (Dellemijn and Vanneste, 1997) but with reduced efficacy compared to nociceptive pain. At high doses opioid tolerance side-effects are a problem.

Adjuvant analgesics form the basis of neuropathic pain drug therapy

Antidepressants: Tricyclic antidepressants are the most effective agents for neuropathic pain. The NNT is about 2.4 for a variety of neuropathic pain states (Sindrup and Jensen, 1999). The newer classes of antidepressants, the selective serotonin-uptake inhibitors and noradrenaline re-uptake inhibitors, have a better side-effect profile but are less effective in neuropathic pain. (Sindrup and Jensen, 1999).

Anticonvulsants: Many small studies and case reports suggest that most anticonvulsants relieve neuropathic pain in some patients. Carbemazepine is of proven efficacy in trigeminal neuralgia with a NNT of 2.6 (McQuay et al, 1995) and remains the treatment of first choice

TABLE 5.
Some neuropathic pain mechanisms and possible sites for therapeutic intervention

Peripheral afferents	Primary afferent specific sodium channels	An increase in sodium channel numbers occurs after nerve injury. Some of these channels are specific to sensory nerves and their selective blockade could offer effective therapy with minimal side-effects. Targets include the tetrodotoxin (TTX) resistant peripheral nerve 3/sensory nerve specific (PN3/SNS) and sodium channels, and the TTX sensitive peripheral nerve 1(PN1) sodium channels
	Sympathetics	Sprouting of sympathetic nerves around dorsal root ganglia and expression of α-adrenoreceptors by damaged peripheral axons occurs after nerve injury. Thus, manipulation of the sympathetic nervous system may play a role in therapy
	Growth factors	Nerve growth factor (NGF) and brain-derived growth factor (BDGF) sensitize primary afferents for nociceptive transmission. Blockade of trkA (NGF receptor) and trk B (BDGF receptor) receptors is potentially therapeutic
	Vanillinoid receptor	Capsaicin is thought to reduce primary sensitization through action on vanillinoid receptors. Work is underway to develop an effective vanillinoid agonist that doesn't produce burning pain on application
Spinal cord mediators	NMDA receptor	NMDA receptor activation plays a central role in central hypersensitivity. Non-specific antagonists like ketamine have widespread effects. Development of more specific antagonists is required
	AMPA receptor	AMPA receptors have been overshadowed to date by NMDA receptors. Topiramate, an anticonvulsant which acts on this receptor, is being studied for use in chronic pain
	Protein kinase Cγ	Protein kinase C is a family of enzymes that catalyse the phosphorylation/dephosphorylation of numerous receptors, altering their activation states. Protein kinase Cγ is upregulated in experimental models of chronic pain. Knockout mice lacking the enzyme fail to develop signs of neuropathic pain. Inhibition of this enzyme may have a role in treating pain
	Neuronal nitric oxide synthase	The postsynaptic terminal releases nitric oxide that diffuses into the presynaptic terminal to cause more neurotransmitter release. Inhibition of nNOS may reduce this positive feedback
	Calcium channel blockers	Calcium flux is important in neurotransmitter release. SN-111 or ziconotide is a N-type calcium channel blocker derived from the marine snail. Early work with SN-111 suggests that N-type calcium blockers may have a future in neuropathic pain treatment. Other animal toxins acting on different classes of calcium channels (e.g. agatoxin from the funnel web spider) also need to be investigated
	Neuronal nicotinic acetylcholine receptor agonists	Epibatidine and ABT-594 have been shown to have pain-modifying properties
	Cannabinoids	The cannabinoid receptor CB1 is highly expressed in the dorsal horn. Cannabinoids suppress pain in animal models of neuropathic pain and anecdotally in humans. Ongoing work on cannabinoids may eventually lead to drugs useful in neuropathic pain
	Purinoceptors (P2X3)	ATP is the main agonist at this receptor. The only licenced antagonist, suramin, has severe side-effects but drugs acting on this site may prove useful in pain therapy
Altered gene expression	c-fos and c-jun	These proteins are expressed in second order neurons after afferent nociceptive input. They are transcription factors that redirect gene expression to produce a sensitized state (i.e. more likely to convey pain). An extreme example of the phenotypic changes that can occur in central sensitization is expression by Aβ mechanoreceptor afferents of substance P — normally solely a C-fibre neurotransmitter. Prevention of the expression of early key transcription factors could retard the development of central sensitization and chronic pain states
Anatomical reorganization	Altered cytoarchitecture	The discovery that Aβ terminals can sprout into C-fibre sites in the dorsal horn following nerve injury may explain some neuropathic pain symptoms

AMPA = α-amino-3-hydroxy-5-methyl-4-isoazolepropionic acid; ATP = adenosine triphosphate; NMDA = N-methyl-D-aspartate; nNOS = neuronal nitric oxide synthase

for this condition. Small studies report the effectiveness of both carbemazepine and phenytoin in painful peripheral neuropathy. However, these drugs are poorly tolerated and have not been perceived to be very effective although widely used. Gabapentin, a newer anticonvulsant with a better side-effect profile, is of proven benefit in a variety of neuropathic pain conditions with NNT figures of 3.2–3.7 (Backonja et al, 1998; Rowbotham et al, 1998). It has recently been licensed for the treatment of neuropathic pain in the UK.

Local anaesthetic-type drugs: Intravenous lignocaine and oral mexiletine have both been shown to reduce neuropathic pain (Kalso et al, 1998; Oskarsson et al, 1997). Mexiletine is not widely used because of adverse effects but is worth trying when other drugs are ineffective.

Tramadol: Tramadol has weak opioid action but most of its analgesic activity is thought to be via inhibition of reuptake of 5-hydroxytryptamine and noradrenaline. Tramadol has a NNT of 3.4 for painful peripheral neuropathy (Sindrup and Jensen, 1999). Adequate studies for other neuropathic pain conditions are yet to be done.

Capsaicin: Topical application of this chilli pepper alkaloid causes burning by releasing substance P from peripheral and central C-fibre terminals. Repeated application desensitizes these fibres. Capsaicin has a NNT of 5.9 for peripheral neuropathic pain states (Sindrup and Jensen, 1999) and is free of systemic effects.

Others: A number of other drug therapies may be tried in various cases of neuropathic pain. These include N-methyl-D-Aspartate (NMDA) antagonists such as ketamine, calcium-channel antagonists, calcitonin, baclofen and levodopa. Until large-scale placebo-controlled trials are performed using these drugs, their use remains experimental.

Nerve stimulation

Transcutaneous electrical nerve stimulation (TENS) is commonly used, has few side-effects and benefits some patients with neuropathic pain. How much placebo effect is involved is unclear.

Spinal cord stimulators have a limited role in treating neuropathic pain. They are most effective for treating ischaemic pain. Implantation of a stimulator is an invasive procedure and should only be undertaken by experts in the field who can provide long-term follow-up care.

Temporary blocks

Nerve blocks with local anaesthetic and an adjuvant designed to have a long lasting therapeutic effect are commonly used in the treatment of neuropathic pain. Epidural nerve block with steroids for radicular back pain and intravenous regional anaesthesia (Biers block) with the addition of guanethidine for complex regional pain syndrome are examples. The efficacy of such blocks remains controversial. Once again, few placebo-controlled studies have been done and those that are reported have loose diagnostic criteria.

Neurolytic techniques

Neurolytic techniques are generally disappointing. Any benefit is usually short-lasting and neuropathic pain returns with a vengeance.

Psychological/behavioural therapy

Psychological and behavioural therapy play a major part in treatment of any chronic pain. The overall goal is to decrease patients' focus on their pain and rehabilitate them to 'normal daily activities'. This reduces patients' pain and improves their quality of life. Counselling, relaxation techniques, distraction techniques, physiotherapy and physical rehabilitation programmes, all play a role. Wells and Miles (1991) reported that half their chronic pain patients reduced drug intake and 29% rejoined the job market after a 4-week rehabilitation programme.

Surgery

Where compression is clearly the cause of neuropathic pain, surgery may be indicated. Examples include carpal tunnel decompression, decompressive laminectomy, and microvascular decompression in trigeminal neuralgia.

NEUROPATHIC PAIN: THE WAY FORWARD

It is imperative that clinicians and neuroscientists work together to study neuropathic pain.

Most patients with chronic pain perceive their pain as a single entity. It is up to the clinicians to identify the separate components of this pain, correlate this with state of the art knowledge gleaned from experimental work and formulate management strategies for all the factors giving rise to pain. A single treatment method, be it pharmaceutical, interventional or psychological, is unlikely to deal effectively with such a complex problem. Multidisciplinary management with constant update of basic science is the way forward.

Neuroscientists must aim to correlate laboratory and animal research with relevant clinical scenarios. Information from comprehensive and meticulous clinical assessment of patients must be incorporated into their work to tease out the

complexities of neuropathic pain. An over-reliance on simplified animal models of neuropathic pain will inevitably lead to many blind alleys and a waste of intellectual and financial resources. HM

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KEY POINTS

- Neuropathic pain is caused by a primary lesion or dysfunction in the nervous system.
- The pathophysiology of neuropathic pain is very complex and remains poorly understood.
- Clinicians dealing with neuropathic pain need to develop a detailed and uniform method of history taking and examination.
- Tricylic antidepressants and anticonvulsants are the best therapeutic agents to date.
- There are many avenues to explore in the search for better treatments. Resources will be best used if basic scientists and clinicians communicate closely.