Neuropathic Pain

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Pain in Neurological Disease

Pain is a frequent symptom of neurological disease. Although there have been improvements in treatment, pain often remains unresponsive to all treatment modalities.

What is Neuropathic Pain?

A limited understanding of underlying pathophysiology, and recent changes in terminology have led to some confusion. The International Association for the Study of Pain (IASP) defines NP as "pains resulting from disease or damage of the peripheral or central nervous systems, and from dysfunction of the nervous system". Originally, NP was used to describe only pain related to peripheral neuropathies, and **central pain** (CP) to lesions of the central nervous system associated with pain. **Neurogenic pain** embraced all causes, both peripheral and central.

The addition of a category of "dysfunction" in the definition of NP allows the inclusion of organic pain states which share the clinical features of NP, but which are not initiated by an identifiable lesion of any part of the nervous system. However, this is a contentious issue; some argue that the "dysfunctional" category should be excluded, on the grounds that there is no initiating neural injury. While it is true that including dysfunctional pain causes difficulties in recognising the limits of NP, exclusion of this important type of pain ignores the clinical reality of the existence of similar pain states, one provoked by neurological damage and the other by damage to non-neural tissues. Creation of a separately defined category of dysfunctional pain is acceptable, as long as it is recognised that there may be pathophysiological mechanisms common to both NP and dysfunctional pain. The debate continues, but from a practical point of view, the current approach to treatment is broadly similar for NP and dysfunctional pain.

The most important of the dysfunctional pain states is **Complex Regional Pain Syndrome** (CRPS, formerly known as Reflex Sympathetic Dystrophy, RSD).

Table 1

Peripheral Causes of Neuropathic Pain

Mononeuropathies and multiple mononeuropathies		
Trauma: compression, transection, post-thoracotomy, painful scars		
Diabetic mononeuropathy and amyotrophy		
Neuralgic amyotrophy		
Connective tissue disease		
Malignant and radiation plexopathy		
Trench foot		
Borreliosis		
Polyneuropathies		
Metabolic/ Nutritional:	Diabetic	Cuban neuropathy
	Alcoholic	Tanzanian neuropathy
	Pellagra	Burning feet syndrome
	Beri-beri	Strachan's (Jamaican) neuropathy
	Amyloid	
Drugs/Toxic:	Isoniazid	Thallium
	Cisplatin	Arsenic
	Vincristine	Clioquinol
	Nitrofurantoin	
	Disulfiram	
Infective:	HIV	
	Acute inflammatory polyneuropathy (Guillain-Barre) / CIDP	
Hereditary:	Fabry's disease	
	Dominantly inherited sensory neuropathy / HSAN	
Malignant:	Myeloma	
	Carcinomatous	
Idiopathic small fibre neuropathy		

Causes of NP

A convenient classification of NP is anatomical, according to the site of initiating nervous system pathology, with an aetiological sub-classification (Tables 1 and 2). A mechanism-based classification is needed, but it is not yet possible to reliably link symptoms and signs to pathophysiology (see Table 4). The development of specific and selective treatments will depend on a mechanism-based classification. For the majority of NP sufferers, the pain will persist lifelong. Co-morbidities (depression, impaired quality of life, employment, domestic issues etc) are very common.

Clinical Features of NP (Table 3)

Patients often find it difficult to describe the quality of NP; it is outside their previous experience of pain. Sensory loss may be mild and overshadowed by **allodynia** (all stimuli producing pain), **hyperalgesia** and **hyperpathia** (delayed perception, summation and painful aftersensation). Rarely, (eg trigeminal neuralgia) there is no demonstrable sensory loss.

There may be signs of **sympathetic dysfunction**, and occasionally dystrophic changes. The onset of pain may be delayed, the commonest example being central post-stroke pain (thalamic), which may start months or years after the initiating stroke.

Pain is often of mixed nociceptive and neuropathic types, for example, mechanical spinal pain with radiculopathy or myelopathy. It is not generally recognised that nociceptive spinal pain can radiate widely, mimicking a root distribution. It can be difficult to identify the dominant pain type and treat appropriately. Such patients require careful examination, imaging and neurophysiological investigation.

Pathophysiology

The pathophysiological properties that are responsible for NP can be broadly categorised into five groups: **ectopic impulse generation** in damaged primary afferent fibres, **fibre interactions, central sensitisation, disinhibition** (failure or reduction of normal inhibitory mecha-

Table 2

Central Causes of Neuropathic Pain

Spinal Root/Dorsal Root Ganglion	
Prolapsed disc	Root avulsion
Arachnoiditis	Surgical rhizotomy
Post-herpetic neuralgia	Tumour
Trigeminal neuralgia	
Spinal Cord	
Trauma including compression	
Syringomyelia and intrinsic tumours	
Multiple sclerosis	
Vascular: infarction, haemorrhage, AVM	
Spinal dysraphism	
Vitamin B 12 deficiency	
HIV	
Syphylis	
Anterolateral cordotomy	
Brain Stem	
Lateral medullary syndrome	Multiple sclerosis
Tumours	Tuberculoma
Syrinx	
Thalamus	
Infarction	Tumours
Haemorrhage	Surgical lesions
Sub-cortical and Cortical	
Infarction	Trauma
AVM	Tumour

Table 3

Clinical Features of Neuropathic Pain

Abnormal pain quality: burning, stabbing, raw, gnawing, sickening
Poorly localised, sometimes diffuse
Paroxysmal pains common
Immediate or delayed onset after injury
Pain intensity altered by emotion and fatigue
Sensory impairment usually in an anatomical distribution
Associated allodynia, hyperalgesia and hyperpathia
Vasomotor and sudomotor changes
Associated dystrophic change in a minority of patients

nisms), and **plasticity** (degenerative and regenerative changes associated with altered connectivity). Table 4 summarises these properties. It is beyond the scope of this short article to discuss pathophysiology in detail, but some important points include:

1. The mechanisms of NP are substantially different to those of nociceptive pain.
2. Novel impulse generators develop at various sites, and these are not stimulus-dependent.
3. In peripheral nerve, it has been shown that ectopic impulse generation (EIG) develops as a result of the expression of abnormal sodium channels. This can be modified by neurotrophic growth factors (a potential target for new treatments).
4. Abnormal chemical sensitivities develop in damaged primary sensory neurons, notably to catecholamines. Whilst this can be readily demonstrated in experimental preparations, the clinical relevance remains uncertain.
5. Degenerative and then regenerative changes in the spinal cord may lead to aberrant connectivity, and possibly a permanently reorganised, irreversible state.
6. Damage at one level in the nervous system may lead to secondary pathophysiological changes at more rostral levels. This has important implications when targeting treatments for NP.

Table 4

Pathophysiology of Neuropathic Pain

1. Peripheral Nerve
Ectopic impulse generation - EIG
(abnormal sodium channel expression)

Increased by:	**Decreased by:**
mechanical stimulation	local anaesthetic
noradrenaline / adrenaline	alpha receptor blockers
ischaemia	axon transport blockers
warming-myelinated fibres	corticosteroid
cooling-unmyelinated fibres	carbamazepine
	phenytoin

2. Dorsal root ganglion
EIG

3. Spinal Nerve Roots
EIG

4. Central Nervous System
Central sensitisation
Dorsal horn neuron "wind up": NMDA receptor mediated
Prostaglandin and nitric oxide synthesis in dorsal horn neurones

Disinhibition
Deafferentation of dorsal horn cells: bursting discharge
Reduced spinal inhibitions: surround, segmental, descending brain stem
Reduced insular cortex inhibition in central pain

Plasticity
Neurotransmitter excitotoxicity: cell death
Post-synaptic receptor up-regulation

Altered Connectivity
Inappropriate regeneration (Growth Associated Protein expression)
Reorganised state

Rostral Effects
Altered physiology at rostral levels resulting from caudal lesions

Complex Regional Pain Syndrome (CRPS)

CRPS is the name now given to reflex sympathetic dystrophy (RSD) and causalgia (Table 5). The term RSD implied a pathogenic role for the sympathetic nervous system that is no longer tenable.

The current definition of CRPS is clinical, and the limits are not clearly drawn (Table 6). As with NP, a mechanism based definition is obviously needed, but is not yet possible.

CRPS is divided into type 1, which includes conditions caused by tissue injury other than peripheral nerve (the majority of cases), and type 2, in which the syndrome is provoked by major nerve injury. The latter corresponds to causalgia, though strictly speaking, causalgia merely means burning pain, and thus denotes a symptom rather than a disease. For the moment, however, the IASP approved terminology makes CRPS type 2 and causalgia one and the same.

The nosology of these conditions is a matter of ongoing debate; the difficulties in finding agreed terms emphasises the limited understanding of their pathophysiology.

The causes of CRPS are listed in Table 7.

Clinical Features and Pathophysiology of CRPS

The common clinical features of CRPS are shown in Table 8. These may vary over time in an individual patient. Not all patients develop dystrophic changes.

The pathogenesis of CRPS is probably heterogeneous; there is evidence of a noradrenergic sympathetic influence on the development of pain, both with and without nerve injury. Chronic inflammatory processes contribute in CRPS type 1; microangiopathic changes have been found in limbs amputated from CRPS sufferers, and anti-inflammatory treatment may help early in the course of the disease. Secondary central sensitisation is an important component of the pain.

Psychological factors have often been suggested in the pathogenesis of CRPS. Patients with conversion disorder and factitious illnesses can present with symptoms closely resembling CRPS. The severe pain of CRPS, with loss of function, produces anxiety and depression in many patients, but there is no evidence that secondary psychological factors developing early after an injury predispose to CRPS.

Prospective studies indicate an incidence of CRPS of about 1-2% after fractures (type 1 CRPS), and 1-5% after peripheral nerve injury (CRPS type 2).

Diagnostic Limits of CRPS

There are no diagnostic tests for CRPS, which is a clinical diagnosis. One of the problems with the current defining diagnostic criteria for CRPS is establishing the limits of the diagnosis. This is at present a matter of clinical judgement, and not surprisingly, opinions differ in relation to individual patients. Three-phase isotope bone scans are frequently abnormal in CRPS, but a normal scan does not exclude the diagnosis.

Table 5

Complex Regional Pain Syndrome (CRPS) Previously Described Syndromes

Reflex Sympathetic Dystrophy (RSD)
Causalgia
Post-traumatic sympathetic dystrophy
Algodystrophy
Sudeck's atrophy
Post-traumatic vasomotor syndrome
Shoulder-hand syndrome

Table 6

Definition of Complex Regional Pain Syndrome (CRPS)

CRPS describes a variety of painful conditions that usually

- follow injury
- occur regionally
- have a distal predominance of abnormal findings
- exceed in both magnitude and duration the expected course of the inciting event
- result in marked impairment of motor function
- are associated with oedema, abnormal skin blood flow, or sudomotor activity in the region of the pain at some time during the course of the illness

(International Association for the Study of Pain, 1999)

Table 7

Causes of Complex Regional Pain Syndrome

Peripheral Tissues
Fractures and dislocations
Soft tissue injury
Fasciitis, tendonitis, ligament strain
Arthritis
Deep vein thrombosis
Prolonged immobilisation of a limb

Peripheral Nerve
Peripheral nerve trauma
Post-ganglionic brachial plexus lesions

Dosal Root
Post-herpetic neuralgia
Spinal nerve root lesions
Brachial plexus avulsion

Central Nervous System
Myelopathies, particularly trauma
Head injury
Cerebral infarction/haemorrhage
Cerebral tumour

Viscera
Abdominal disease
Myocardial infarction

Idiopathic
No identifiable provoking cause

Treatment of Neuropathic Pain

NP due to a compressive lesion may be completely relieved by surgery, particularly if there has been little damage.

However, there may be severe continuing NP with relatively minor damage (eg root compression). For the majority of patients with NP, the realistic goal of treatment, undertaken in a multidisciplinary pain clinic, is partial analgesia, and an improvement in functional status.

The modalities of treatment used for NP are listed in Table 9.

Local and Regional Treatments

In some circumstances, local measures may be sufficient, but many patients will also require systemic drugs.

In the presence of severe allodynia, treatment may not be tolerated in the affected area, but applied in adjacent areas, these measures may be helpful.

Topical local anaesthetic applications are often partially effective in allodynia. Topical capsaicin, which initially stimulates, then desensitises afferent C fibres, is helpful in a minority of patients; many find the initial burning pain intolerable.

A successful local anaesthetic block, for example to a painful scar, may be repeated, combined with corticosteroid which can increase the duration of pain relief, possibly by reducing EIG (see Table 4).

Since Leriche reported that causalgia could be dramatically relieved by surgical sympathectomy, temporary blocking or permanent interruption of the noradrenergic sympathetic efferent supply has become an accepted treatment for causalgia and other post-traumatic neuralgias, for CRPS, and for some CP.

Temporary partial analgesia lasting hours or days is commonly observed, and a small number of patients seem to benefit from repeated blocks over long periods. However, controlled trials have not shown significant benefit from any type of sympathetic blockade.

Electrical Spinal Cord and Deep Brain Stimulation

Spinal cord (dorsal column) stimulation (SCS) may be helpful in patients with pain due to major limb injury, CRPS affecting a limb, plexopathies, thoracic or post-herpetic neuralgia, and occasionally, thoracic myelopathies. The commonest indication is lumbar disease with spinal pain, persistent root pain and arachnoiditis (the majority of whom have had at least one operation). The mode of action is thought to be activation of dorsal horn and possibly thalamic gating mechanisms.

SCS can provide lasting useful analgesia in a minority of patients with NP, but in many, the duration of analgesia is only weeks or months, due either to technical factors, or changing physiology.

The principal indication for deep brain stimulation, targeting a number of sites in the thalamus, is severe central post-stroke pain. As with SCS, the analgesic effect may be short-lived.

Systemic Drugs

The quality of trials of systemic drugs for NP has undoubtedly improved in recent years, and several systematic surveys help to guide treatment. The number needed to treat (NNT) statistic, defined as the number of patients needed to treat to produce one patient with 50% pain relief, is commonly used in these meta-analyses. However, this statistic masks variability in trial design and methodology, pain measures (including quality of life measures), and duration of treatment. Table 10 lists systemic, local and spinally administered drugs found to have an analgesic effect in NP, with NNTs where it is possible to calculate these. Excluding trigeminal neuralgia, the two leading treatments for NP are amitriptyline / nortriptyline, and gabapentin. Amitriptyline has multiple sites of action; one possible mechanism in NP may be a facilitation of the descending serotoninergic analgesic pathway from the brain stem to the dorsal horn. Gabapentin has an action on voltage dependent calcium channels in spinal cord interneurones.

Opioids are considerably less effective in NP than in nociceptive pain, but the previous dogma that opioids are without effect in NP has been modified in view of new evidence from controlled trials. In patients with severe intractable NP, a trial of opioid therapy (controlled release morphine or fentanyl patches) is justified when other treatments have failed.

Reports of relief of post-herpetic neuralgia with intrathecal methyl prednisolone require confirmation.

Surgery for NP

NP results from damage to the nervous system, and that includes surgical trauma, even carefully placed lesions designed to relieve pain. Anterolateral cordotomy leads to contralateral analgesia, and this produces short-term analgesia. But when performed for pain of non-malignant origin, a proportion of patients will develop NP in the distribution of the lesioned tract, months or years later. The same applies to surgical lesions of peripheral nerve, root or spinal cord, advocated for the relief of chronic pain. Thalamotomy, with lesions at various sites, often produces short duration analgesia. Thus, therapeutic lesioning for NP are now considered obsolete by most authorities.

Psychological Treatment

Patients with intractable NP are frequently depressed, and may benefit from antidepressant drugs. Behavioural measures, and pain management programmes are helpful for many patients, both as adjunctive treatment and as the sole treatment, when all other physical measures have failed.

Table 8

Clinical Features of Complex Regional Pain Syndrome

Inflammatory:	pain colour change temperature change limitation of movement exacerbation by exercise oedema	
Neurological:	allodynia hyperpathia incoordination tremor	involuntary muscle spasms paresis pseudoparesis
Dystrophic:	skin nails	muscle bone
Sympathetic:	hyperhidrosis changed hair and nail growth vasomotor abnormalities	

Table 9

Treatment Modalities for Neuropathic Pain

Topical:	local anaesthetic capsaicin
Local:	transcutaneous electrical stimulation (TENS) acupuncture thermal (heat, cold) vibration massage
Blocks:	somatic of nerve, plexus, root sympathetic of ganglia, or regional guanethidine
Central stimulation:	spinal cord stimulation (SCS) deep brain stimulation (DBS)
Spinal drugs:	epidural or intrathecal (local anaesthetics, opioids)
Systemic drugs:	see Table 10
Surgery:	decompression
Psychological:	behavioural measures, pain management programmes
Rehabilitation	

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Table 10

Drug Treatment of Neuropathic Pain: Controlled Trials

Drug/Route	Condition	Efficacy
Systemic:		
Tricyclic antidepressants	PHN	+ NNT=2.3
	DPN	+ NNT=3.0
	NP	+
	HIVN	-
SSRI: paroxetine	DPN	+ NNT=6.7
citalopram	CPSP	-
Carbamazepine	TN	+ NNT=2.6
	DPN	+
	CPSP	-
Phenytoin	DPN	+
Gabapentin	PHN	+ NNT=3.7
	DPN	+ NNT=3.2
Mexiletine	DPN	+/- less than 50% analgesia
Baclofen	TN	+
Fentanyl	NP	+
Oxycodone	PHN	+
Dextromethorphan	DPN	+
	CPSP	-
Phentolamine	NP	+/-
Topical lignocaine	PHN	+
Topical capsaicin	PHN, DPN	+
Topical non-steroidal anti-inflammatories	PHN	+
Epidural clonidine	NP/CRPS	+
Intrathecal methyl prednisolone	PHN	+
Regional guanethidine	CRPS	-
Intranasal calcitonin	CRPS	+/-

Abbreviations: PHN = post-herpetic neuralgia. DPN = painful diabetic neuropathy. NP = neuropathic pain. HIVN = painful HIV neuropathy. CPSP = central post-stroke pain. TN = trigeminal neuralgia. CRPS = complex regional pain syndrome. NNT = number needed to treat.