

# Chronic neuropathic pain: A clinical perspective

by Paul Austin

## Introduction

Chronic neuropathic pain is not a single entity, but refers to a heterogeneous group of pain conditions that are surprisingly common in clinical practice; with an estimated prevalence of 8-17% in the general population [1, 2]. Specific treatment options for neuropathic pain are severely lacking, with less than half of patients receiving adequate pain relief. Furthermore, neuropathic pain greatly impairs quality of life and is a major economical problem, costing the Australian economy in the region of \$5 billion per year, due to loss of working days and healthcare costs [3, 4].

## Clinical definition and causes

The current definition for chronic neuropathic pain from the International Association for the Study of Pain is “*Pain arising as a direct consequence of a lesion or disease affecting the somatosensory system*” [5]. Where the term ‘disease’ refers to the presence of an identifiable pathological process, while ‘lesion’ refers to macro- or microscopically identifiable damage, and ‘somatosensory system’ refers to the neurons that detect sensory stimuli from the skin and internal organs. The definition of ‘chronic’ tends to be determined by an arbitrary length of time since onset, the most common are 3 or 6 months. However, a better description is perhaps pain lasting longer than the expected period of recovery. Neuropathic pain should be further quantified as being of peripheral or central origin in terms of the location of the lesion or disease, as they have distinct clinical manifestation and underlying pathophysiology. As such there are four broad classes of neuropathic pain according to underlying etiology and anatomical location;

- (i) Painful peripheral neuropathies, again sub-divided into;  
*Focal or multifocal*, due to; traumatic injury, surgery or amputation (e.g., phantom-limb pain).  
*Generalized*, due to; infection (e.g., postherpetic neuralgia), metabolic or nutritional conditions (e.g., diabetes or alcoholism), toxins (e.g., arsenic or chemotherapy), or hereditary conditions (e.g., Charcot-Marie-Tooth disease).
- (ii) Central pain syndromes, due to; stroke, multiple sclerosis (MS), spinal cord injury, Parkinson’s disease or traumatic brain injury.
- (iii) Complex painful neuropathic disorders (e.g., complex regional pain syndrome, CRPS).
- (iv) Mixed pain syndromes, combining elements of non-neuropathic (nociceptive) and neuropathic pain (e.g., chronic lower back pain with radiculopathy).

One of the most common causes of painful peripheral neuropathy is routine surgery, and due to the requirement for ongoing patient care, significant data exists on the prevalence of neuropathic pain in this cohort. Unfortunately however, this data only highlights how common chronic neuropathic pain is, despite post-operative management and injury healing. For example, following inguinal hernia repair or

Caesarean section 10% of patients report ongoing pain and disabilities 6 months after surgery; following mastectomy or lumpectomy 20-30% of women report chronic pain; following amputation, thoracotomy or coronary bypass surgery 30-50% report persistent pain [6].

### **Symptoms of Neuropathic Pain**

Unsurprisingly the major symptoms of chronic neuropathic pain are pain-related and have also been termed 'sensory hyperphenomena'. These sensory hyperphenomena include; spontaneous (i.e., not stimulus induced) persistent pain and spontaneous shooting and electric shock-like pain; unpleasant sensations (dysaesthesia/paraesthesia), such as a feelings of ant crawling, burning, tingling (pins and needles) and wetness; pain resulting from normally non-painful stimuli (allodynia), such as touch or mild heat; and an exaggerated painful response to painful stimuli (hyperalgesia), such as heat or cold. Of these symptoms, spontaneous pain is probably the best clinical marker of neuropathic pain being present in all cases of peripheral neuropathy, postherpetic neuralgia and CRPS, whereas thermal allodynia and pinprick hyperalgesia are only present in in 30-40% of these conditions [7]. Another essential part of neuropathic pain is a paradoxical deficit (partial or complete) of sensation, which may be adjacent to, or intermingled with, areas of sensory hyperphenomena. The sensory deficits may involve all sensory modalities, but a loss of temperature and mechanical sensation appears critical. For example, in post-stroke pain, studies suggest that sensory deficit is necessary for the occurrence of pain, whilst characteristic features of central pain caused by spinal cord injury are sensory loss and areas of hyperalgesia [8].

Comorbidities affecting normal physiology and behaviour are also commonplace in the neuropathic pain patient; for example, up to 60% have moderate to severe depression and over 70% report less than optimal sleep quality [7]. However the full list of comorbidities also includes; metabolic and endocrine disturbances, changes in appetite, disturbances of familial and social relations, reduced cognitive and memory function, loss of libido, reduced movement, loss of interest in pleasurable activities (anhedonia), loss of the ability to cope effectively with stress and anxiety. As you can imagine for the majority of chronic pain sufferers these complex behavioural and physiological disruptions are equally, if not more, debilitating than the pain [8-13].

### **Mechanisms of Neuropathic Pain**

In terms of understanding the mechanisms of chronic neuropathic pain, significant research has focused on the properties of neurons following peripheral nerve or spinal cord injury, ultimately leading to the proposal of both peripheral and central 'sensitisation' as critical disease mechanisms. Sensitisation in this sense refers to changes in activity state of the neurons of the somatosensory system, such that abnormal signals from both injured and intact neurons result in amplification of responses to painful and non-painful stimuli. Peripheral and central amplification is mediated by injury-induced (i) altered expression of molecules which enhance painful signals, such as sodium channels and neurotransmitters (e.g., Substance P, glutamate), (ii) increased neuronal excitability due to direct activation by immune mediators (e.g., cytokines), (iii) decreased threshold for neuronal firing and ectopic nerve firing, (iv) autonomic neurons, which don't normally carry pain, coupling to pain-carrying

neurons, and (v) altered synaptic transmission and connectivity in the spinal cord, particularly due to loss of inhibitory neurons, which normally inhibit pain signals [See reviews for more detail 14, 15, 16].

### **Treatment of Neuropathic Pain**

Unfortunately current treatment of neuropathic pain is less than ideal, with fewer than 50% of patients experiencing satisfactory pain relief and tolerable side-effects [17]. This often results from the prescription of drugs with no proven efficacy for their particularly condition or when they do receive appropriate treatment, they receive less than effective dosages. Although there are no drugs that have been specifically designed to treat neuropathic pain, several previously licensed drugs have shown some efficacy, and are now considered first-line treatments for neuropathic pain. These include; antidepressants, particularly tricyclic antidepressants (TCAs, e.g., desipramine) and selective serotonin and norepinephrine dual reuptake inhibitors (SSNRIs, e.g., venlafaxine); antiepileptics (e.g., gabapentin and pregabalin), and local anaesthetics (e.g., topical lidocaine) [17]. Opioid analgesics (e.g., morphine and oxycodone) and tramadol, so effective to treat nociceptive pain, are generally used as second-line treatments or in combination with first-line treatments for neuropathic pain, although in certain clinical circumstances, such as neuropathic cancer pain, they are effective first-line therapies [17]. Third-line treatments include certain antiepileptics, for example, carbamazepine, which is effective for trigeminal neuralgia, whilst antidepressants, bupropion, citalopram, and paroxetine, are recommended for patients benefitting from antidepressants other than TCAs or SSNRIs, particularly where there is comorbid depression or anxiety. Despite a number of drugs showing some efficacy for neuropathic pain, many patients go without adequate relief from this debilitating condition. Tellingly, none of these drugs were designed to treat neuropathic pain, therefore research which focuses on drugs that specifically target the underlying causes of neuropathic pain are likely to dramatically improve relief from pain and comorbid behavioural disabilities.

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