Acute Neuropathic Pain Following Surgery

Dr Robert David Searle

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The candidate confirms that the work submitted is his own, except where work which has formed part of jointly-authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

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Chapter 5 Are patients with poorly controlled postoperative pain more likley to have neuropathic symptoms and signs?

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Abstract

Chronic neuropathic pain occurring after an operation is a common problem, however little data is available describing the nature or prevalence of acute neuropathic pain following surgery. In this thesis, I explore the measurement scale properties of a commonly used neuropathic pain screening tool, and use this tool to describe the prevalence of acute and chronic neuropathic pain following thoracic surgery. I also explore how best to diagnose acute neuropathic pain with a Delphi survey of expert opinion and confirmatory observational cohort study. The results show that the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) neuropathic pain screening tool demonstrates acceptable fit to the Rasch measurement model in the chronic postoperative pain population, but only has reliability consistent with use at a group level. Using this tool, I demonstrate that 8% of thoracic surgery patients experience acute neuropathic pain an average of 3 days after surgery, with 22% developing neuropathic pain by 3 months. Experiencing acute neuropathic pain significantly increased the odds of developing chronic neuropathic pain (odds ratio 7.7 [95% confidence interval 1.5-39.7]). A Delphi survey of specialists identified 9 items considered important in the diagnosis of acute neuropathic pain, and suggests that unlike diagnosis in the chronic pain population, a poor response to opioid medications was an important indicator of neuropathic pain. Preliminary results from a matched cohort study confirm this, by demonstrating that verbal descriptors of neuropathic pain are significantly more common in patients with poorly controlled postoperative pain despite strong opioid use.

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Abbreviations

BDNF	Brain Derived Neurotrophic Factor
CCK	Cholecystokinin
CNS	Central Nervous System
CRPS	Complex Regional Pain Syndrome
DIF	Differential Item Functioning
DN4	Douleur Neuropathique en 4 questions
EFNS	European Federation of Neurological Societies
EMG	Electromyography
EQ-5D	EuroQol health related outcome measure
GABA	Gamma-aminobutyric acid
IASP	International Association for the Study of Pain
IQR	Inter-quartile range
LANSS	Leeds Assessment of Neuropathic Symptoms and Signs
MRI	Magnetic Resonance Imaging
NeupSIG	IASP special interest group on neuropathic pain
NMDA	N-methyl D-aspartate
NNT	Number needed to treat
NPQ	Neuropathic pain questionnaire
NPS	Neuropathic pain scale
NRS	Numerical rating scale
NSAIDS	Non-steroidal anti-inflammatory drugs
NYHA	New York Heart Association
OR	Odds ratio
PCA	Patient controlled analgesia
PHN	Post herpetic neuralgia
QST	Quantitative sensory testing

RR	Relative risk
S-LANSS	Self report LANSS
SNRI	Selective noradrenaline reuptake inhibitor
TCA	Tricyclic antidepressant
TRP	Transient receptor potential
TRPV	Transient receptor potential vallinoid
VAS	Visual analogue scale
VATS	Video assisted thoracoscopic surgery
WHO	World Health Organisation

1 Introduction

1.1 Acute pain following surgery

The history of surgery, anaesthesia and pain management are inextricably linked together through developments in medicine that have occurred during the last two centuries. The discovery in the mid nineteenth century, that the sedative gases ether, chloroform and nitrous oxide could relieve the suffering associated with surgery and childbirth coincided with a shift away from the prevalent philosophy that pain and suffering were inevitable, or that pain was inflicted by God to strengthen faith.[1] As these advances in medicine facilitated the practice of ever more complex surgery, the acceptance that the relief of bodily pain was a positive good grew. At the same time as these advances in anaesthesia and surgery were occurring, pharmaceutical and technical advances meant that the availability of analgesics steadily increased. In the early nineteenth century, Morphine was first derived from opium and subsequently manufactured by the pharmaceutical company Bayer. The development of the hollow syringe in the mid nineteenth century made the administration of morphine simple, and it's potent analgesic properties mean it is still the mainstay of postoperative pain relief regimes today.[1] Aspirin was released in the early twentieth century, and there followed a proliferation of analgesic drugs and techniques over the subsequent century. During this time, acute postoperative pain management has become increasingly recognized as a vital part of modern medical practice. However, despite advances in our understanding of the pathophysiology of acute pain, and a burgeoning variety of pain management techniques and medications, many people still experience significant pain following surgery. One reason why this may be so is explored in

this thesis, however first it is necessary to establish some important definitions regarding the nature and extent of pain in this context.

The most prevalent definition of pain results from the International Association for the Study of Pain (IASP) workforce on taxonomy [2]:

"An unpleasant sensory or emotional experience associated with actual or potential tissue damage, or described in terms of such damage."

Traditionally, pain has been sub-classified in a number of ways, for example by diagnosis (malignant/non malignant), by timescale (acute/chronic) or by mechanism (nociceptive/neuropathic).

1.1.1 Acute Pain – definitions

Acute pain has been defined in a number ways, but with common themes that include a usually time limited physiological response to an identifiable injury. Interestingly, the terms "acute pain" and "chronic pain" do not appear in the IASP taxonomy of pain terms, nevertheless these terms are in widespread use in both clinical practice and pain research.[2] The absence of a consensus definition, does however mean that subtle variations in meaning exist throughout the literature. The following are common examples of such definitions:

"Pain of recent onset and probable limited duration. It usually has an identifiable temporal and causal relationship to injury or disease." [3]

"The normal, predicted physiological response to an adverse chemical, thermal or mechanical stimulus….associated with surgery, trauma and acute illness." [4]

"Pain that is present in a surgical patient after a procedure. Such pain may be the result of trauma from the procedure or procedure related complications." [5]

The temporal nature of pain symptoms is also commonly used to distinguish acute from chronic pain, with arbitrary chronological markers of between two and six months historically used as cut off points for the progression of acute to chronic pain.[6] There are obvious conceptual issues with defining pain as acute one day and chronic the next according to a temporal cut off point, with expert opinion acknowledging that pain associated with new tissue injury may last less than one month, but at times greater than six months.[2] Therefore in recent years there has been a move towards describing acute pain according to both time and physical pathology, with acute pain tending to last a limited period of time, and remitting once the underlying pathology resolves.[6]

In the case of postoperative pain therefore, we can conclude that acute pain represents the 'initiation phase' of a cascade of pathophysiological events triggered by tissue injury, which generally resolves as the injury heals, although this may take a variable length of time, and in some individuals progress to chronic pain even when the underlying surgical insult has resolved.[7] As well as unpleasant sensory phenomena, pain after surgery is also related to unpleasant emotional and mental experiences.[8]

1.1.2 Acute pain – epidemiology

Despite progressive improvements in the understanding and options available to treat acute postoperative pain over the last sixty years, the evidence suggests that many patients still experience an unacceptable degree of pain

after surgery. Table 1.1 outlines the incidence of poorly controlled postoperative pain since early studies on this topic were published in the 1950's.

Since the development of early acute pain services in the 1980's there have been many national and international attempts to improve postoperative pain control. These include attempts to improve assessment (for example by highlighting pain as the "fifth vital sign"), treatment (for example by developing practice guidelines), and widespread promotion of the deficiencies in acute pain management (such as the IASP "Global year against acute pain 2010-2011").[5, 9] Nevertheless, a significant proportion of patients still experience moderate to severe pain following their operation, and this has seemingly remained unchanged from 1950 through to the present day. The reasons behind such a lack of progress are likely to be multifactorial. Proposed causes include under measurement of pain, deficiencies in the education and training of healthcare workers, poor compliance with guidelines and underuse of effective analgesic techniques.[10-13]

Reference	Incidence of moderate or severe pain or insufficient analgesia (%)
Papper et al., (1952)[14]	33
Lasagna et al., (1954)[15]	33
Keeri-Szanto et al., (1972)[16]	20
Cronin et al., (1973)[17]	42
Banister (1974)[18]	12-26
Tammisto (1978)[19]	24
Cohen (1980)[20]	75
Donovan (1983)[21]	31
Owen et al., (1990)[22]	37
Apfelbaum et al., (2003)[23]	70
Sommer et al., (2008)[24]	41
Maier et al., (2010)[25]	29.6-55

Table 1.1 The incidence of moderate or severe acute postoperative pain or insufficient analgesia 1950 to 2010 (modified from the 'Report of the working party on pain after surgery' [26]).

1.2 Neuropathic pain

Although the classification of pain into 'acute' or 'chronic' is ubiquitous both in pain literature and also clinical practice, over the last two decades a more fundamental, mechanism based classification of pain has emerged. This 'mechanistic' approach led to the classification of pain into that related to tissue damage (nociceptive pain) or pain related to nervous system injury or dysfunction (neuropathic pain).[27]

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

"Pain caused by a lesion or disease of the somatosensory nervous system."[2]

In contrast, nociceptive pain is defined as:

"Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors."[2]

In contrast to neuropathic pain, nociceptive pain implies pain that occurs as a result of a normally functioning nervous system. Importantly, although these definitions are widely accepted, they do not represent diagnostic criteria.

Although this mechanistic approach to pain classification is a relatively modern construct, there are many historical references to neuropathic pain. One of the earliest descriptions of peripheral neuropathic pain depicts symptoms akin to tic douloureux in the distribution of the radial nerve as a result of a musket ball injury during the Spanish Peninsula War.[28] By the 20th century, neuropathic pain caused by lesions of the central nervous system was well described, with the term 'central pain' coined by Behan in 1914.[29] For most of the 20th century, pain regarded as arising from a damaged or dysfunctional nerve was termed 'neuralgia', with the phrase 'neuropathic pain' first appearing in the 1980's. Since the first edition of the IASP taxonomy of pain in 1986, the term 'neuropathic pain' has become widespread in both pain research and clinical practice.[30]

1.2.1 Neuropathic pain – epidemiology

Neuropathic pain is a relatively common symptom of a variety of disorders that affect both the peripheral and central nervous systems. Table 1.2 shows the prevalence of neuropathic pain among individuals with different medical problems.

Condition	Neuropathic pain prevalence %
Diabetes[31]	11-26
Cancer[32, 33]	18-39
HIV[34, 35]	35-53
Back Pain[36]	37
Infection[37]	10-25
Stroke[38]	8
Spinal cord injury[39]	75
Multiple Sclerosis[40]	58

Table 1.2 The reported prevalence of neuropathic pain in specific medical conditions

It is clear from the table that neuropathic pain plays a role in the experience of pain symptoms for a wide variety of disparate medical conditions. Importantly, neuropathic pain is not only associated with diseases of the nervous system, where we would perhaps expect pain to be of a neuropathic nature, but also disease processes where a mixed pathology is more likely. For example, neuropathic pain is surprisingly prevalent amongst cancer pain patients.[32] In a recent international study of over 1000 cancer patients 79.7% were given the clinical diagnosis of nociceptive pain, and 16.9% considered to have neuropathic pain.[41] Of note, up to 39% of cancer pain patients may have a dual

pain mechanism, both nociceptive and neuropathic, a common feature of other conditions such as lower back pain.[33, 36]

The prevalence of neuropathic pain in the general chronic pain population is approximately 17%, demonstrating that a neuropathic pain component is commonly seen amongst chronic pain patients.[42] Perhaps more surprising is the prevalence of neuropathic pain in the general population, with an estimated prevalence of 6-8% when using screening questionnaires.[42, 43]

In general, neuropathic pain seems to be associated with particularly poor health related quality of life, with mixed neuropathic pain having a similar impact on the EQ-5D as NYHA Class IV heart failure.[44] Patients also seem to suffer greater pain intensity, and report greater impact on daily living compared with nociceptive pain.[45] Even when controlling for pain intensity, neuropathic pain patients seem to suffer more mental and physical health problems, implying that the nature, and not simply the intensity of neuropathic pain is contributory.[46] The impact of neuropathic pain on quality of life is in part likely to reflect the chronic nature of such pain in many conditions. Although there is a paucity of longitudinal data describing the natural history of neuropathic pain, for some conditions such as diabetic peripheral neuropathy, symptoms are unlikely to improve with time (with 77% continuing to have pain problems 5 years after diagnosis in one study).[47] In contrast, where the initiating disease or lesion resolves, such as post herpetic neuralgia, symptoms may be more likely to improve over time.[48]

1.2.2 Neuropathic pain – pharmacological management

A mechanistic approach to classifying pain is important, as there are differences in the approach to managing neuropathic compared to nociceptive pain. In terms of pharmacotherapy, traditionally conditions thought to be associated with a predominantly nociceptive pain component, such as arthritis, have been treated with analgesics such as paracetamol, non-steroidal anti-inflammatory drugs (NSAIDS) and weak or strong opioids.[49] Similarly, this approach has been the cornerstone of analgesic management of cancer pain for over two decades following the publication of the WHO analgesic ladder.[50]

In contrast, neuropathic pain tends to be managed with entirely different types of medications, designed to act as pharmacological modulators of nerve pain. The most commonly used classes of drugs for neuropathic pain are the antidepressants (including tricyclic antidepressants and serotonin and noradrenaline reuptake inhibitors [SNRI]), and the anticonvulsants (including the gabapentinoids and older drugs such as carbamazepine). Antidepressant drugs act by enhancing the descending inhibitory pain pathways from the brain to the spinal cord. Anticonvulsants have a variety of mechanisms including blockade of sodium and calcium channels in the central nervous system. Current National Institute for Clinical Excellence (NICE) guidance for the management of neuropathic pain includes tricyclic antidepressants, gabapentinoids and SNRI medications as first and second line management.[51]

Although these medications are relatively efficacious for managing neuropathic pain, they seem to have little benefit in conditions where nociceptive pain predominates. For example, a recent Cochrane systematic review of the efficacy of antidepressants in inflammatory arthritis concluded it was not

possible to draw firm conclusions about the efficacy of these drugs.[52] Similarly, six unpublished trials investigating the efficacy of gabapentin for the treatment of nociceptive pain failed to show a benefit, although this has not been widely publicized by the drug manufacturers, and the full trial details are not available.[53]

The evidence therefore suggests that antidepressant and antiepileptic medications are effective for neuropathic pain, but not effective treating nociceptive pain. It should be of no surprise therefore, when these drugs are used in populations where there are high levels of mixed pain (such as cancer pain) systematic reviews demonstrate that such adjuvants are helpful, although the effect size is much smaller than that seen in patients with non-cancer neuropathic pain.[54]

Interestingly, some analgesics commonly used to treat nociceptive pain are also effective treating neuropathic pains. For example, tramadol, with its dual mode of action (opioid agonism and enhancing descending inhibitory pain pathways) is considered a third line anti-neuropathic agent by NICE, and is commonly used to treat nociceptive pain.[51, 55, 56] Similarly, strong opioids such as morphine or oxycodone also show efficacy in treating neuropathic pain, although outside the cancer pain population are rarely considered first or second line agents due to the potential for adverse effects.[46]

Neuropathic and nociceptive pain are therefore discrete pain entities, with differing health impact and responding to different modes of analgesia.

1.3   Neuropathic pain following surgery

The pathophysiology of postoperative pain is complex, and includes elements of nociceptive (generated by the noxious stimulus of surgery), and inflammatory (resulting from tissue injury and immune cell activation) pain processes.[57] There is also evidence from research into the mechanisms of postoperative pain that support the hypothesis that part of the postoperative pain experience may be neuropathic.

There appear to be a number of mechanisms by which surgery may result in neuropathic pain. Broadly, these include direct nerve injury (including by mechanisms other than obvious nerve trauma), and perhaps more controversially, via the process of central sensitization.

1.3.1   The pathogenesis of postoperative nerve injury

Signs of nerve damage are well documented in a number of surgical procedures where nerves cross, or are in close approximation to the surgical field. This includes chest wall surgery (both thoracic and breast surgery), hernia surgery and mandibular osteotomy.[58-61]

During thoracic surgery, nerve damage can occur during the dissection of the muscle layers, intercostal muscle incision, rib retraction or suturing of intercostal muscles during thoracotomy.[62] Rib retraction causes allodynia in animal models of post thoracic surgery pain, and some patients exhibit objective signs of nerve damage such as loss of superficial abdominal reflexes, and changes to neurophysiological studies.[63-65] Maguire et al., (2006) investigated intercostal nerve damage at the time of operation with nerve conduction studies, and demonstrated two patterns of nerve injury.[66] They suggest this may reflect

different mechanisms of injury; neuropraxia resulting from pressure related to rib retraction and damage caused by traction on the nerve.[66] More recently, detailed quantitative sensory testing of patients six months following thoracotomy revealed nerve injury to be a common phenomenon.[67]

Inguinal hernia repair similarly risks damage or disruption to major peripheral nerves including the ileoinguinal, ileohypogastric and genitofemoral nerves.[68] Quantitative sensory testing demonstrates that sensory disturbance following surgery is common, implicating that nerve damage around the time of surgery has occurred.[68] As well as direct damage to nerves at the time of hernia surgery, an inflammatory response to implanted mesh has also been implicated in postoperative nerve damage.[69, 70]

Breast surgery is also linked to high levels of post-operative sensory disturbance. In patients who have had breast surgery to treat cancer, the prevalence of sensory disturbances range from 31% to 85%, depending on the treatment received, with axillary lymph node dissection a particular risk factor.[71] This is perhaps unsurprising given the close proximity of the intercostobrachial nerve to lymph nodes in the axilla. However, a number of studies have tried to define the role of this nerve in the generation of chronic pain following breast cancer surgery, with mixed results.[72-76] Methodological problems probably account for this result, with none of the studies using objective measures such as quantitative sensory testing.[71] Sensory changes are also common following cosmetic breast surgery, with one questionnaire based study revealing 75.8% of respondents had sensory changes over the breast, a mean of 31.8 months following breast augmentation surgery.[61]

Although less common, sensory changes or other evidence of nerve damage is present following many other types of surgery. For example, a minority of hip surgery patients experience femoral neuropathy (0.1-2.4%) as a complication of surgery.[77] Interestingly, although quantitative sensory testing of patients with chronic pain following hip arthroplasty revealed hyperalgesia over the operation site, intact thermal sensation suggests nerves with cutaneous innervation over the hip are not implicated, rather the findings may reflect damage to deeper tissues (such as muscle).[78]

This conclusion is interesting in light of other recent findings, which suggest that mechanisms other than overt, major peripheral nerve damage may be implicated in the generation of neuropathic pain following surgery. The suggestion that the sensory hyperalgesia present following hip arthroplasty may be a result of muscle or deep tissue damage is supported by experiments investigating 'neuropathic muscle pain' in animal models.[79] Alvarez et al provide experimental evidence that persistent muscle hyperalgesia is present in animal models of painful neuropathy.[79] This suggests that neuropathic pain arising from muscles may be a greater clinical problem than is generally appreciated, and may contribute to the development of neuropathic pain following surgery.[80]

The preceding evidence suggests that overt peripheral nerve injury following surgery is possible, and that damage to other tissue such as muscle can also trigger changes associated with nerve damage and neuropathic pain. There is also evidence that the skin incision alone may be enough to trigger nervous system changes normally seen with injury to peripheral nerves.[81]

Hill et al., (2010) demonstrate that in animal models, skin incision can induce expression of nerve injury and regeneration associated genes.[81] Specifically, they demonstrate that nerve regeneration related genes (such as activating transcription factor 3) that are normally absent from dorsal root ganglion neurons, but present following peripheral nerve injury, are also induced by skin incisions.[81] Skin tissue contains resident nerve axons, and it seems injury to these may be enough to trigger expression of neuronal injury/regeneration genes. This may represent a further mechanism by which neuropathic pain changes can be triggered following surgery; however to what extent this contributes to clinical symptoms and signs remains unknown. Certainly, the size of skin incision alone does not appear to affect acute pain following total hip arthroplasty.[82] Dorr et al compared a minimally invasive surgical approach with a more conventional approach to hip arthroplasty, yet with the same skin incision size.[82] They demonstrated significantly less postoperative pain in the minimally invasive group where underlying muscles were preserved.[82] In a complementary study, there was no difference in postoperative pain when different skin incision lengths were compared (with the same degree of deep tissue injury).[83]

The immune response to surgery has also been implicated in the pathogenesis of postoperative nerve damage.[84] Staff et al., (2010) report a series of patients who developed postoperative neuropathy with an inflammatory rather than mechanical cause.[85] Patients presented following a variety of procedures with focal, multifocal or diffuse neuropathies, with pain a common feature of presentation. An inflammatory cause was confirmed by nerve biopsy, which typically showed axonal degeneration and focal fibre loss with increased

epineural perivascular lymphocytic inflammation. Patients also had abnormal MRI changes, demonstrating increased T2 signal and nerve enlargement in the implicated roots, plexus or peripheral nerve. The authors note that some cases of inflammatory neuropathy clinically mimic mechanical postoperative neuropathies, and that inflammatory causes of postoperative nerve damage are probably under-recognised (the prevalence of this condition is unknown).[85] Interestingly, chronic pain following a thoracotomy for lung transplant is much less prevalent than following thoracotomy for other reasons (5% and >40% respectively.[86] One potential reason may be the immune suppression received by transplant patients.

In addition to nerve injury caused by direct trauma from a surgical incision, or inflammatory response, perioperative neuropathy may arise as a complication of the need for anaesthesia. In a retrospective analysis of over 380,000 surgical cases performed at a single institution over a 10 year period, Welch et al (2009) discovered 112 episodes of perioperative nerve injury that were not a direct complication of the surgery itself.[87] Upper limb injuries were more common, as were primarily sensory symptoms (rather than motor dysfunction).[87] They also reported a significant association between nerve injury and hypertension, type of anaesthetic and surgical specialty.[87] The overall frequency of nerve injury was 0.03%, lower than studies performed in the 1970's (0.14%) and late 1980's (0.11%).[88, 89]

A variety of factors have been implicated in the aetiology of 'anaesthetic' nerve damage, including patient positioning, and direct damage from regional or neuraxial anaesthetic procedures. Surgical positions, such as the lithotomy position, have been implicated in obturator, lateral femoral cutaneous, sciatic

and peroneal nerve damage following surgery, with nerve strain and increased compartment pressures potential causes.[90-92] Other nerves, such as the ulna, are prone to damage because of their prominent and superficial location.[93]

Nerve damage may also occur as a result of regional anaesthetic techniques. This may result from direct needle trauma, injection into the nerve or from neurotoxic drugs or chemicals used in the procedure.[94] Long term nerve damage is rare, confounding attempts at reliably measuring its prevalence (0.5-1% in retrospective studies), although transient symptoms of neuropraxia may be more common (8-10%).[94-96]

In summary, there are a number of different processes by which nerve damage may occur in the perioperative period. They include damage to skin, muscle or nerve by the surgical incision or retraction, anaesthetic related factors and inflammatory processes. It is useful to review how such nerve damage may result in neuropathic pain, and how the complex processes involved in neuropathic pain generation differ from those driving the nociceptive pain experience.

1.3.2   The pathophysiology of neuropathic pain

A number of physiological processes occur following nerve injury. Some of these processes are regarded as maladaptive, and demonstrate the plasticity of the nervous system in response to an insult such as surgery. These maladaptive processes are complex, but help us explain the clinical features of neuropathic pain following nerve injury.

Spontaneous pain

Spontaneous pain that arises without stimulus is a feature of neuropathic pain. A number of mechanisms by which spontaneous pain may be generated have been discovered. When a nerve is injured, ectopic action potential generation can occur at the site of the neuroma, at the injured nerve's dorsal root ganglia and in neighbouring uninjured primary sensory neurons.[97]

Spontaneous firing of action potentials occurs as a result of increased expression or altered trafficking of voltage gated sodium channels, both in injured and uninjured neurons.[98, 99] Exactly which subtype of sodium channel is implicated is not clear, mainly because there are no animal models of spontaneous pain.[97] As an example of the difficulties investigating this process, $Na_{v1.8}$ sodium channels are thought to have an important role in generating neuropathic pain, however $Na_{v1.8}$ 'knockout' mice do not exhibit reduced neuropathic pain behaviour, and $Na_{v1.8}$ seems to be down regulated following axonal injury.[99-102] The dorsal root ganglion may have a role in regulating this ectopic activity, with the hyperpolarization-activated cyclic nucleotide-modulated channel (HCN) implicated in raising membrane excitability.[103] Further changes in the dorsal root ganglion alter the responsiveness, transmission and survival of sensory neurons.[104]

Distal to the nerve injury, denervated Schwann cells help generate molecules such as cytokines and growth factors, which increase axonal sensitivity by increasing sodium and TRP channels. Inflammatory mediators, (such as TNFα), which gather around the injured neuron further increase ectopic activity.[105-107]

Gene transcription appears to have a major role in driving the processes that signal nerve injury and the resulting production of local mediators.[97]

A further generator of spontaneous pain following nerve injury may be body temperature.[97] Following nerve injury, TRPV1 channels in nerve axons, which are normally triggered by noxious heat, may have their thresholds for triggering reduced to that of normal body temperature.[108] Normal body temperature may therefore become a noxious stimulus, resulting in the experience of spontaneous pain.

Stimulus evoked pain

In neuropathic pain states, the nervous system is hypersensitive to normal sensory input. A number of changes following nerve injury seem to facilitate this response, with the dorsal horn of the spinal cord an important area of neuronal plasticity and sensitization. In particular, the balance between inhibitory and excitatory nerve activity is profoundly altered at this level.

Sensory inflow to the dorsal horn is altered after peripheral nerve damage resulting in the eventual death of inhibitory interneurones.[109] These interneurones inhibit pain transmission by modulating presynaptic input, and regulate postsynaptic transmission through effects on the neurotransmitters GABA and glycine.[97] Death of these interneurones would result in loss of GABA and glycine control, a process that produces evoked neuropathic pain symptoms in animal models.[110] Descending inhibitory pain pathways are also disrupted by nerve injury. These pathways extend from areas of the brain involved in pain processing (anterior cingulate gyrus, amygdala and hypothalamus), through the brainstem to the spinal cord, and help to modulate

pain signals via the neurotransmitters serotonin, noradrenaline and endogenous opioids.[97] Following nerve injury, there is loss of this inhibitory effect, which may transform from inhibition to facilitation.[111] Other inhibitory processes are also affected by nerve injury. There is reduced expression and sensitivity of opioid receptors in primary afferent neurons and the dorsal horn of the spinal cord.[97] Brain derived neurotrophic factor (BDNF) released by microglia causes alterations in chloride ion transport across membranes in the dorsal horn. Consequently the normal inhibitory effects of GABA receptor activation no longer result in membrane hyperpolarization.[112]

Concurrent increase in excitatory transmission occurs, as a result of presynaptic alterations in the synthesis of neurotransmitters and changes in receptor density, and postsynaptic phosphorylation of NMDA receptors facilitate onward pain signaling. In particular, there is marked up-regulation of $\alpha_2\delta$ subunit voltage gated calcium channels in the dorsal horn and elsewhere (including the dorsal root ganglion) in response to nerve injury.[97, 113] This structure appears to be involved in new excitatory synapse formation mediated via thrombospondin (an astrocyte secreted protein that promotes new synapse formation in the CNS), and is the target for the anti-neuropathic drugs gabapentin and pregabalin.[114]

A further example of a stimulus evoked symptom in neuropathic pain is allodynia, whereby a normally non-noxious stimulus (such as light touch) produces pain.[2] Following peripheral nerve injury, Aβ fibres, normally responsible for touch sensation, transfer their inputs to pain circuits in the spinal cord.[97] This may occur as a result of structural changes in the dorsal horn of the spinal cord. Aβ fibres normally terminate in laminae III – V of the dorsal horn,

with pain signaling Aδ and C fibres terminating in levels I and II. Peripheral nerve injury promotes the expression of genes associated with nerve regeneration in order to aid the reconnection of separated axons.[97] This tendency towards nerve growth was thought to be responsible for sprouting of uninjured Aβ axons into neighbouring dorsal horn laminae, which are normally responsible for pain transmission, with Aβ inputs to the spinal cord therefore resulting in onward pain transmission.[115, 116] Subsequent studies however showed that the Cholera toxin used to demonstrate the effects of 'sprouting' of Aβ axons into neighbouring dorsal horn laminae, is also taken up and transported by injured C fibres. This probably accounts for the novel labeling in lamina II of the dorsal horn seen after nerve injury, rather than aberrant nerve growth into adjacent areas.[117, 118]

Immune system responses to nerve injury, may also be responsible for the nervous system hypersensitivity seen in neuropathic pain.[119] Microglial cells are activated in the dorsal horn following nerve injury, and release immune mediators, which contribute to the activation and maintenance of neuropathic pain by altering nerve function, producing pain hypersensitivity.[97]

A number of processes affecting numerous locations within the pain pathway are triggered following nerve injury. It is clear that many of these changes give rise to the features of neuropathic pain, however, to what extent do these processes differ from nociceptive or inflammatory pain models?

1.3.3 Central sensitization

Although it is clear that nerve injury causes changes in the central nervous system that facilitate pain transmission, and lead to features such as

hyperalgesia and allodynia, confusingly, a similar picture can occur following nociceptive pain. This has been termed central sensitization, and is a feature of both nociceptive and neuropathic pain.

In the 1960's it was discovered that repetitive stimulation of a nerve at a constant C-fibre strength resulted in a steady increase in action potential firing in the dorsal horn.[120] This was one of the first examples of use dependent plasticity within normally functioning pain pathways of the central nervous system and was termed 'wind-up'. Subsequently, it was discovered that activation of peripheral nociceptors increased synaptic efficacy in dorsal horn nociceptors, which long outlasted the initial stimulus.[121, 122] Furthermore, not only was the conditioning input amplified in this way, but also was non stimulated input (both nociceptive and non nociceptive) from other nerve fibres.[122] This homosynaptic and heterosynaptic potentiation was termed 'central sensitization'. The increase in dorsal horn synaptic strength is mediated via excitatory amino acids, alteration in ion channel properties, increased receptor density and activation of pre and postsynaptic kinases.[97] Immune cells (microglia), astrocytes and alteration in gene transcription help to maintain the sensitized state, where normal inhibitory inputs are reduced, and excitatory activity increased.[122]

These discoveries raised the possibility that once triggered by a nociceptive event, the central nervous system was capable of changing, distorting or amplifying pain even when the original noxious stimulus resolved.[122] Pain in this state is uncoupled from peripheral nociceptive stimuli and becomes centrally driven. Rather like the changes in the dorsal horn that occur with neuropathic pain, amplification and strengthening of afferent inputs is such that normally

innocuous inputs such as Aβ touch sensations can activate pain circuits resulting in allodynia.[122] A further feature is secondary hyperalgesia, which occurs in areas beyond the site of injury.[104]

There is evidence that central sensitization occurs following surgery. In the immediate postoperative period, patients can experience secondary hyperalgesia, with no spread in thermal sensitivity, suggesting initiation of central sensitization.[123, 124] Researchers have also found evidence of central sensitization contributing to chronic pain post hernia repair pain, elicited with QST.[125] In general, patients with central sensitization may present with dynamic tactile allodynia, secondary hyperalgesia and temporal summation.[122] As we have seen, these are also features of neuropathic pain, unsurprising considering it is also driven by a process of central sensitization, all be it with the trigger of nerve injury rather than the barrage of peripheral nociceptive afferent that also occur following surgery. Central sensitization, even if it is initiated by nociceptive pain, can no longer be termed 'nociceptive pain', as it may occur in the absence of noxious stimuli.[122] Neither can it be called 'neuropathic pain' which requires a demonstrable disease or lesion of the somatosensory nervous system, despite the overlap in symptoms such as allodynia and hyperalgesia. Rather it reflects a maladaptive central nervous system response, which can be driven by both nociceptive and neuropathic pain resulting in a state of induced pain hypersensitivity.[122]

Central sensitization has been implicated in the development of chronic pain following surgery. For example, there appears to be a relationship between the extent of secondary hyperalgesia experienced in the immediate postoperative setting following abdominal surgery, and the development of chronic pain.[126, 127]

Similarly, signs of central sensitization are found in 51% of patients with chronic post surgical pain, compared to 15% of pain free patients.[125, 128]

1.3.4 Opioid induced hyperalgesia

Like central sensitization, opioid induced hyperalgesia is a further pathological state presenting with symptoms that may overlap those of neuropathic pain in the postoperative period.

Both acute and chronic administration of strong opioids appears to trigger changes similar to those of central sensitization and neuropathic pain in susceptible individuals.[129] The NMDA receptor has been implicated in this process, with increased receptor activity present after chronic morphine administration, and NMDA receptor antagonists attenuating the development of opioid induced hyperalgesia.[130-132] Other mechanisms that may be involved include changes in the descending inhibitory pain pathways of the central nervous system towards facilitation rather than inhibition of nociceptive signaling.[129] Peripheral nerve changes also occur, with the TRPV1 receptor likely to play a role in the development of hyperalgesia.[129]

The key clinical feature of opioid induced hyperalgesia is a paradoxical increase in pain in response to administration of a strong opioid analgesic. In addition, the central and peripheral nervous system changes outlined above can result in symptoms similar to those found in neuropathic pain, including hyperalgesia and allodynia.[129] Opioid induced hyperalgesia has been demonstrated in both healthy volunteers and also the acute postoperative setting, and therefore represents a further confounding factor when diagnosing acute neuropathic pain.[133, 134]

1.3.5 The epidemiology of postoperative neuropathic pain

The evidence reviewed so far suggests that nerve injury, via a number of mechanisms, occurs following surgery, and that this nerve injury can trigger a number of changes in the nervous system that result in neuropathic pain. What is the clinical evidence that neuropathic pain following surgery occurs?

The existence of chronic pain following surgery has been recognized for many years, although there has been increasing recognition of this problem in the last 15 years, with a resulting proliferation of research articles on this topic (a literature search on the topic for a recent systematic review initially returned 6512 articles).[135] Nerve damage has long been implicated in the development of this chronic pain following surgery. For example, Blades and Dugan (1944) describe pain following thoracic surgery for wounds inflicted during the second world war as 'intercostal pain' and identify nerve damage at the time of operation as the likely causative agent.[136] Despite such early recognition of the problem, there are comparatively few research articles describing the prevalence specifically of chronic neuropathic pain following surgery. Using the example of thoracic surgery (thoracotomy or video assisted thoracoscopy), prior to 2007 (when the research on this area presented in this thesis was undertaken), only 2 studies had estimated the prevalence of probable or definite chronic neuropathic pain following surgery (according to subsequently published diagnostic criteria).[66, 137, 138] A further 14 studies either used sufficient pain descriptors or screening tools which allowed an estimate of the prevalence of 'possible' neuropathic pain.[135] A subsequent systematic review in 2013, which also included research on sternotomy patients, identified 45 papers which allowed an estimate of the prevalence of possible, probable or definite

neuropathic pain after thoracic surgery.[135] It is clear that in a relatively short period of time, interest in this topic has accelerated.

Assessing the true prevalence of neuropathic pain following surgery is challenging. Firstly, there are no universally agreed diagnostic criteria for neuropathic pain, and a variety of methods have been used in published studies. These include diagnosis by an experienced pain physician, neuropathic screening tools (of which there are a number), or the use of objective tests such as QST. Secondly, a variety of time points have been used to assess prevalence ranging from 6 weeks to 35 years.[135]

In their comprehensive systematic review on this topic, Haroutiunian et al., (2013) describe the prevalence of chronic neuropathic pain following thoracic surgery, breast surgery, groin hernia repair, and total hip or knee arthroplasty (THA/TKA).[135] They graded papers according to whether or not the diagnostic criteria in each paper met recently published standards, or whether neuropathic pain was diagnosed by other methods, and gave a prevalence for each.[138] The results of this review are presented in figure 1.1.[135]
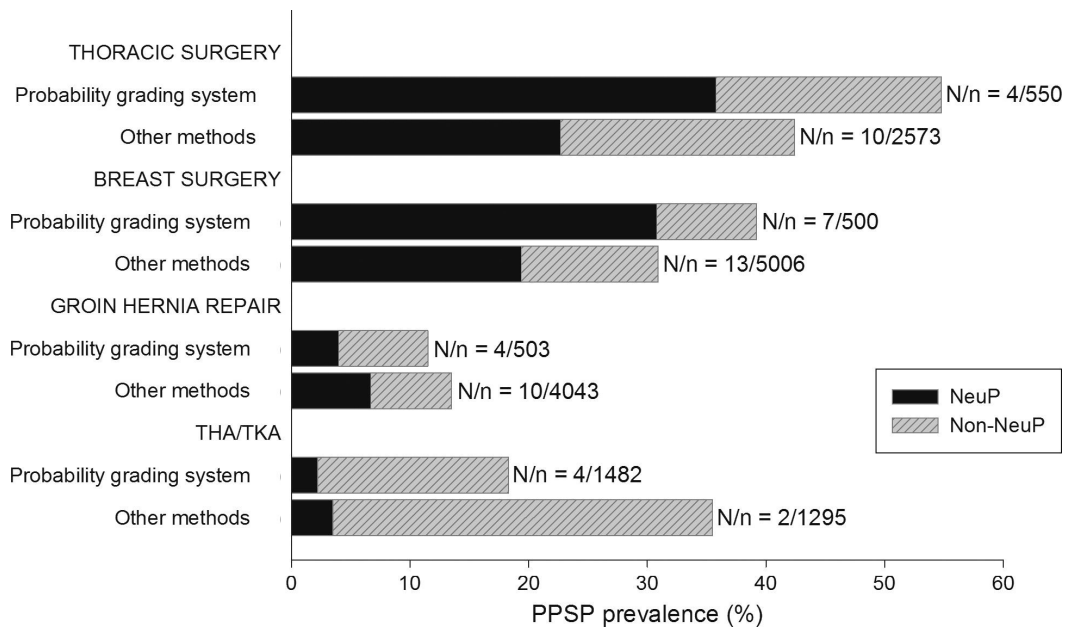
Figure 1.1 Results of a systematic review of studies investigating the prevalence of chronic postoperative neuropathic pain following different types of surgery (from Haroutiunian et al, 2013)

N = number of studies included, n = number of patients, NeuP = neuropathic pain, PPSP = Persistent Post Surgical Pain, TKA = total knee arthroplasty, THA = total hip arthroplasty, Probability grading system = neuropathic pain diagnosed using a method consistent with a published diagnostic consensus statement[138], Other methods = Other methods of neuropathic pain diagnosis (e.g. neuropathic pain screening tools).

From this study, it is clear that surgery around the chest wall results in a high prevalence of chronic neuropathic pain. For thoracic surgery, of the 34.5% of patients who experience chronic postoperative pain, 52-66% have neuropathic pain. The picture is similar for breast surgery (chronic pain prevalence 31%), where 68-74% of those with pain have neuropathic pain.[135] Pain is less common in areas where major peripheral nerve damage is more unlikely, such as following knee or hip arthroplasty (19.8%) and also less likely to be neuropathic (6-9%).

Interestingly, figure 1 demonstrates that the prevalence of neuropathic pain using both strict methods of diagnosis (including objective signs of nerve damage) and more descriptive methods is similar for chest wall surgery, but differs for groin and orthopaedic surgery.[135] For the latter two, using descriptive

methods of diagnosing neuropathic pain seems to elicit a much greater prevalence than using a diagnostic method with more objective criteria.[135] One possible explanation for this would be that the descriptive method of diagnosis is eliciting people whose pain is maintained by central sensitization as well as those with neuropathic pain.

Neuropathic pain as a component of chronic postsurgical pain has been described following a number of other procedures not included in the above systematic review. These include craniotomy (25%), amputation (>80%) and caesarean section (53%).[139-141]

Interestingly, it is clear from the epidemiological data that not everyone with postoperative nerve damage goes on to develop chronic neuropathic pain. Evidence of sensory dysfunction following surgery can be surprisingly prevalent in the pain free population. Aasvang and Kehlet (2010) demonstrated 20% of pain free post hernia repair patients had sensory dysfunction.[128] Sensory dysfunction was even more common in pain free individuals following thoracic and breast surgery (43% and 37% respectively).[61, 142] This may present an additional confounding factor when trying to accurately estimate postoperative neuropathic pain prevalence, and is perhaps evidence of a genetic susceptibility to developing neuropathic pain.

The natural history of postoperative neuropathic pain is not well described. In a retrospective questionnaire survey of women undergoing breast surgery over a 5 year period in Aberdeen, Smith et al., (1999) discovered that 58% of women with pain reported declining symptoms, 9% had increasing pain symptoms and 33% had variable symptoms.[143] Although attempts were made to limit the

analysis to those with neuropathic pain, the results are limited by the varying time interval between surgery and receiving the questionnaire (time since surgery was not reported). Interestingly, in a follow-up study using the same cohort of patients 7-12 years after their original surgery, of those reporting chronic pain in the original study, 52% continued to have pain, with the symptoms resolving in 48%.[144] This suggests that although for some people postoperative neuropathic pain resolves with time, for a significant proportion it continues to be a problem many years after the original surgery. One study investigating the prevalence of painful phantom breast pain following mastectomy suggests neuropathic pain may increase with time (from 12.7% at 1 year to 17.4% at 6 years).[3] In contrast, most studies investigating chronic postsurgical pain of all causes (without determining the nature of the pain) tend to report a decline in pain symptoms with time.[145-148]

Although there is considerable research into the prevalence of chronic neuropathic pain following surgery, there is very little published data describing the onset of postoperative neuropathic pain, in particular whether neuropathic pain occurs in the acute postoperative pain setting.

1.4   Acute postoperative neuropathic pain

The temporal onset of neuropathic pain following surgery is poorly described. Traditionally, acute postoperative pain has been considered to be nociceptive in origin. However, there is both preclinical and clinical evidence that neuropathic pain may play a role in the acute pain experience.

1.4.1 Preclinical evidence for acute postoperative neuropathic pain

The spinal nerve ligation animal model is traditionally considered a neuropathic

pain model, however it also involves surgery and triggers an inflammatory

response linked to pain behaviour.[149] Experiments using this model have

demonstrated marked hyperalgesic pain behaviours in the ipsilateral limb of

affected rats by postoperative day 3, and increased spontaneous and ectopic

pain fibre discharges, associated with allodynia, by day 7.[150, 151] In a rat model

of thoracic surgery (which includes thoracotomy and rib retraction),

Buvanendran et al., (2004) demonstrate that rats who go on to develop long

lasting chronic neuropathic pain behaviour begin to demonstrate signs of

mechanical and cold allodynia early in the postoperative period.[63] This pain

model was designed to mimic the prolonged rib retraction and subsequent

intercostal nerve compression that occurs during thoracic surgery, and therefore

represents a convincing model of surgery with likely peripheral nerve damage.

Symptoms of neuropathic pain began on day 2 following surgery, with rats

exhibiting mechanical and cold allodynia. By day 10 the 50% of rats who

developed long lasting neuropathic pain following the surgery all had

established neuropathic pain symptoms.[63]

In contrast, animal models of postoperative pain designed to mimic surgery

without peripheral nerve damage seem less likely to elicit signs of neuropathic

pain. For example, the skin/muscle incision and retraction (SMIR) model,

performed on the inner thigh of rats, does not evoke heat hyperalgesia or cold

allodynia (mechanical allodynia was not possible to assess due to the site of

surgery).[152]

These animal models suggest that for some individuals, neuropathic pain may contribute to their pain experience in the early postoperative period. Unfortunately, animal models of pain whilst useful for exploring pathophysiological processes are perhaps less reliable when assessing pain symptoms.[97] Subjective symptoms cannot be assessed directly in animal models; instead surrogate markers that rely on motor activity (such as withdrawal) are used. In particular, there are no preclinical models that directly measure key neuropathic symptoms such as spontaneous pain.[97]

Nevertheless, animal models are useful indicators of pain, even though they may never replicate the full complexity of the human pain experience. Certainly, there is evidence that tactile allodynia measured in rats corresponds with neuropathic mechanical hypersensitivity in humans, and that anti-neuropathic medications reduce these symptoms in rats just as they do in humans.[97, 153-155]

1.4.2 Clinical evidence for acute postoperative neuropathic pain

Acute neuropathic pain has been described following a number of different clinical conditions. For example, in a longitudinal study of pain symptoms in 73 patients following spinal cord injury, Sidall et al., (2003) report that over 50% had symptoms of 'at level' or 'below level' neuropathic pain beginning in the first 2 weeks following injury.[39] In an earlier study in spinal cord injury, the authors report that 78% of patients had developed allodynia by 2 weeks following injury.[156] Neither study measured symptoms or signs at a time point earlier than 2 weeks.

The picture is less clear in other medical examples of neuropathic pain. Herpes zoster infection can cause the classical neuropathic pain associated with post

herpetic neuralgia (PHN). Patients with herpes zoster infection typically experience a prodrome of dermatomal pain symptoms before the characteristic rash appears.[157] The prodromal pain qualities may include the paraesthesias and dysaesthesias present in neuropathic pain.[157] Some patients may go on to develop a continuum of pain symptoms through the acute phase, subsequently developing post herpetic neuralgia.[158] Patients who experience pain in the first 30 days following rash have been described as suffering from 'acute herpetic neuralgia'.[159] However, controversy exists over whether or not acute herpetic neuralgia and chronic post herpetic neuralgia have the same underlying pathophysiological drivers, and it may be that the acute pain owes much of its experience to a post-infective inflammatory process.[157] Nevertheless, studies investigating the treatment of acute herpetic pain have shown responsiveness to the anti-neuropathic agent gabapentin, supporting the role of neuropathic pain in the acute pain experience.[160]

Traumatic injury to peripheral nerves also causes neuropathic pain, and there are case reports of military personnel injured in battle experiencing acute neuropathic pain.[161] In a study of 50 army casualties, Mercer et al (2009) found that 28% of patients had neuropathic pain in the first week following injury, with a further casualty developing neuropathic pain during the second week following injury.[162]

It seems from these examples that neuropathic pain can develop during the acute phase following injury or disease to the nervous system. Unfortunately, few potential causes of neuropathic pain are planned, or have definitive starting points (for example diabetic peripheral neuropathy), which makes examining the time course of neuropathic pain difficult, particularly determining when

neuropathic symptoms and signs begin. Surgery is one exception to this, therefore making it an ideal population to study. It is clear that some procedures have a high prevalence of chronic postoperative neuropathic pain and demonstrable nerve injury, and the onset of injury is known about.

Pain experts have commentated on the existence of acute postoperative neuropathic pain, however there is a paucity of data to support this.[163-165] In a retrospective survey of 408 patients who received mastectomy for breast cancer, Smith et al., (1999) enquired about onset of symptoms of post-mastectomy pain syndrome (considered by them to be a neuropathic pain experience) via postal questionnaire.[143] Thirty percent of those patients surveyed remembered immediate onset of post-mastectomy pain, 25% had onset within a month of surgery and 15% had an onset between 1-3 months following surgery.[143] Only 24% reported onset of symptoms outside the acute post-operative time period. Unfortunately, this result may be biased by a number of factors. Firstly, the pain experienced immediately following the operation may have been nociceptive or inflammatory pain rather than neuropathic post-mastectomy pain. Secondly, the retrospective nature of the survey meant that some patients were being asked to recall details that occurred 6 years ago, potentially introducing further inaccuracies. Lastly, many women received adjuvant treatment for their cancer (such as chemotherapy and radiotherapy), which has also been shown to cause neuropathic pain, making the assumption of a surgical cause for symptoms potentially unsound. Nevertheless, this early report raises the suggestion that some patients may experience neuropathic pain early in the postoperative period.

Interestingly, the severity or intensity of acute postoperative pain has been shown to be a risk factor for the development of chronic postoperative pain. In a retrospective survey of women who had breast surgery, Tasmuth et al., (1996) discovered that those with chronic pain following surgery remembered more severe acute pain following their surgical procedure compared to those who did not go on to develop chronic pain.[166] A prospective study in thoracic surgery patients confirmed this finding, with results that suggested a predictive relationship between pain at 24 and 48 hours following surgery, and the development of long term pain.[167] Moving beyond the first 48 hours following surgery, in a prospective case series of patients having inguinal hernia repair, Callesen et al., (1999) discovered that those with high pain scores 1 week following surgery had a higher risk of suffering moderate or severe pain 12 months later.[168] Similar findings exist for non-surgical trauma, such as serious injury and childbirth.[169, 170] These findings are interesting, as we know from population based studies that neuropathic pain tends to be more severe, or of greater intensity than nociceptive pain.[45] Coupled with the knowledge that a significant proportion of chronic postoperative pain patients have neuropathic pain, it would seem logical to hypothesize that the more intense pain experienced by some people in the acute postoperative period may indicate the development of acute neuropathic pain, which subsequently becomes chronic.

Further evidence for the existence of acute postoperative neuropathic pain may come from examining the response of postoperative pain to analgesics specifically designed to target neuropathic pain. Although published data is lacking, it would seem likely that gabapentin is not an effective drug in the treatment of nociceptive pain.[53] However, it does seem to have an analgesic

effect on acute postoperative pain. A single dose of gabapentin for established moderate or severe postoperative pain is superior to placebo, although has a number needed to treat to reduce pain by 50% (NNT) of 11 (compared to a NNT of 4 in neuropathic pain).[171] When used in conjunction with other analgesic agents in the postoperative period, systematic reviews and meta-analyses show that the gabapentinoids have a significant opioid sparing effect.[172, 173] The fact that these drugs do not appear effective in nociceptive pain, yet do have an effect on acute postoperative pain suggests that at the very least the acute postoperative pain experience may be one of mixed nociceptive/neuropathic pain, or that a minority (reflected by the NNT of 11) may experience significant neuropathic pain that responds to these analgesics.

So, there is mounting evidence to support the hypothesis that some people may experience acute postoperative neuropathic pain. There is however, very little published data describing this problem.

Hayes et al., (2002) conducted a prospective survey of patients referred to an acute pain service over a 2 ½ year period.[174] Patients considered to have unexpectedly high levels of pain intensity were investigated for the possibility of acute neuropathic pain. During the survey period, 4888 patients were seen by the acute pain service, and 51 (1%) identified as suffering from neuropathic pain.[174] The survey reported that neuropathic pain occurred immediately after the precipitating event in 24% of cases, with 67% reporting delayed onset and the remaining patients unsure of onset time.[174] Of the 51 patients identified with neuropathic pain, 27.5% resulted from surgery. Interestingly, 41 patients were followed up at six months (with 10 lost to follow up) with 78% reporting persisting pain.[174] Although this study seems to confirm that acute neuropathic

pain following surgery occurs, there are a number of confounding factors that make estimating the prevalence of this using their methodology potentially unreliable. Firstly, only patients who were referred to the acute pain service were considered, and then only if they had unexpectedly high pain intensity scores were they examined for neuropathic pain symptoms and signs. A number of patients would therefore not be recognised, including those with 'normal' pain scores, patients not referred to the acute pain service and those patients who had day surgery (and therefore went home). Secondly, some patients (notably lower limb amputation patients) were excluded from the survey because of other ongoing research. Thirdly, the authors diagnosed neuropathic pain without using a validated method. Fourthly, patients with pre-existing neuropathic pain were not excluded from the study, potentially skewing results. Lastly, it is not clear at what time point following the initiating event patients were assessed. Data describing the onset of symptoms appears to be based on patient recollection rather than objective assessment. There are therefore a number of methodological flaws that confound accurate prevalence data for acute neuropathic pain following surgery.

1.5   Summary of research problem

The preceding evidence demonstrates that nerve damage occurs as a consequence of surgery, and that a significant proportion of patients seem to develop chronic neuropathic pain as a result of this. The time course describing the onset of neuropathic pain is not well described. Although animal studies and human case reports described the phenomenon of acute neuropathic pain, there is no accurate measure of the prevalence of this condition. Indeed, it is not clear if a neuropathic component to the acute pain experience can be

reliably distinguished from the nociceptive pain barrage that is likely to predominate following surgery. Investigating acute neuropathic pain is important, as evidence shows that despite advances in the treatment of pain over the last century, acute pain remains poorly treated and is a risk factor for the development of long-term pain problems. Neuropathic pain is commonly treated with specific medications such as anticonvulsants and antidepressants, and identifying neuropathic pain in the immediate post-operative setting may allow targeted treatment using these medications to help reduce the burden of poorly controlled pain.

The aim of this thesis is to investigate the diagnosis and prevalence of acute neuropathic pain following surgery.

1.5.1 Aims and objectives

In order to accurately assess the prevalence of acute neuropathic pain, it is necessary to consider how neuropathic pain is diagnosed and measured. The second chapter of this thesis will review the methods of diagnosing neuropathic pain, with the specific aim of evaluating the modern psychometric properties of the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) neuropathic pain screening tool.

Further aims of this thesis are to estimate the prevalence of acute neuropathic pain, in a population of thoracic surgery patients thought likely to be at risk of developing this problem. An additional aim is to assess whether patients with acute neuropathic pain are at risk of developing chronic neuropathic pain 3 months after surgery.

Additional objectives of this thesis are to explore how, in the face of a paucity of published data on the subject, acute neuropathic pain is diagnosed by acute pain specialists, with the specific aim of achieving an expert consensus on the symptoms and signs considered important in this diagnosis.

A final aim is to confirm this consensus opinion by clinical investigation of post-operative patients. This is presented as a pilot study for a matched cohort evaluation of neuropathic symptoms and signs in two groups of acute pain patients, with the specific aim of assessing the odds of developing neuropathic symptoms and signs in patients with poorly controlled acute post operative pain (despite the use of strong opioids) compared to those with well controlled acute post-operative pain.

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2   The diagnosis and assessment of neuropathic pain

The term 'neuropathic pain' has been in common usage amongst clinicians and in pain research for over twenty years, however for much of this time controversy has existed surrounding the correct definition and diagnostic criteria for this condition. Indeed the term 'neuropathic pain' is essentially a clinical description, and lacks formal diagnostic criteria. Confusingly, even the definition of neuropathic pain has changed between the research presented in this thesis beginning and ending. Clearly, such lack of consensus makes research in the area of neuropathic pain prevalence complicated.

The development of neuropathic pain screening tools has allowed a reproducible way of estimating the prevalence of neuropathic pain in the research and clinical setting. This chapter will therefore review how neuropathic pain is diagnosed and examine the properties of neuropathic screening tools.

It was hypothesized that one such screening tool, the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) (appendix 1) would demonstrate unidimensionality and interval level measurement properties when examined using modern psychometric techniques. The specific aims of the research presented in this chapter were to analyse LANSS data collected from a cohort of chronic pain patients, including those with post surgical pain, using Rasch analysis to investigate scale unidimensionality, fit to the Rasch model and differential item functioning.

2.1   The definition of neuropathic pain

The definition of 'neuropathic pain' has changed significantly since it first

emerged as part of a mechanism based classification of pain. In 1994 The

International Association for the Study of Pain (IASP) published the second

edition of it's internationally recognized taxonomy of pain, including a definition

of neuropathic pain as:

"Pain initiated or caused by a primary lesion or dysfunction of the nervous

system"[2]

This definition of neuropathic pain has been criticized for a lack of specificity,

particularly the inclusion of 'dysfunction' within the definition.[175, 176] For example,

it could be argued that the process of central sensitization seen after tissue

injury, (but not specifically linked to nerve damage) could be regarded as a

dysfunctional response of the nervous system, blurring the definition of

neuropathic pain with other mechanisms of pain generation.[175] Complex

Regional Pain Syndrome (CRPS) type 1 was a further example of diagnostic

confusion, as the symptoms and signs of this condition indicate nerve

dysfunction, in the absence of a nerve lesion. Whilst some clinicians describe

this as a neuropathic pain condition, others felt strongly that it was not.[176]

The 1994 IASP definition of neuropathic pain was therefore felt to lack both

diagnostic specificity and anatomic precision.[138] In particular, as understanding

of the pathophysiology of processes such as central sensitization improved, it

was felt that neuropathic pain needed to be distinguished from secondary

nervous system changes arising from nociceptive pain.[138] Furthermore, it was

felt necessary to have a definition of neuropathic pain, which helped eliminate

other pain generators that commonly occur in patients with nerve lesions (such as spasticity).[138]

As a result of these concerns, the Special Interest Group on Neuropathic Pain (NeupSIG) subgroup of the International Association for the Study of Pain, published a consensus document in 2008 setting out a revised definition of neuropathic pain and a diagnostic grading system.[138] The revised definition of neuropathic pain was:

"Pain arising as a direct consequence of a lesion or disease affecting the somatosensory nervous system" [138]

In this definition, the controversial term 'dysfunction' is replaced with the word 'disease' in order to exclude nervous system changes that occur as a result of normal nociceptive pain processing. The reference to 'nervous system' in the original definition, was replaced with 'somatosensory nervous system' in order to exclude pain that arises as a secondary consequence of nerve damage, such as spasticity or muscle rigidity. This definition was subsequently adopted in guidelines on neuropathic pain assessment, and later replaced the 1994 definition of neuropathic pain in the IASP taxonomy of pain in 2011.[177-180]

This new definition of neuropathic pain has aroused criticism over the restrictive nature of limiting this condition to lesions or diseases of the somatosensory nervous system, and in particular the exclusion of CRPS as a neuropathic pain condition under the new guidelines.[181-183] Furthermore, the need to demonstrate a lesion or disease of the nervous system is regarded by some as impractical for conditions where pain is the primary symptom and specific nerve lesions are less obviously demonstrated with imaging or neurological tests. [184, 185]

Examples of conditions that fall into this category include postsurgical pain and cancer pain, and it has been argued that for many clinicians the diagnosis of the type of pain (nociceptive or neuropathic) precedes the diagnosis of the lesion.[185]

The definition of neuropathic pain has therefore undergone subtle change in the last five years. However, the definition is simply a description of a clinical condition and does not in itself provide a method for diagnosing neuropathic pain. As pain is a subjective experience there has been a lack of objective gold standard criteria for diagnosing the underlying pain mechanism. For many years a diagnosis of neuropathic pain was made based on clinical information and an understanding of pain classification, with little specific diagnostic guidance available. Increasing recognition that common groups of symptoms and signs may have discriminant diagnostic value, led to the development of screening tools to aid the bedside diagnosis of neuropathic pain and provide a reproducible method for diagnosing pain mechanisms in research projects.

In an attempt to establish further diagnostic clarity, the 2008, revised definition of neuropathic pain also proposed a method of grading the diagnosis of neuropathic pain according to history, examination and the presence of confirmatory neurological testing.[138] The certainty of diagnosis would be subsequently graded possible, probable or definite.

Unsurprisingly, as the definition of neuropathic pain has evolved over the last twenty years, so have the methods for diagnosing this condition. In the continued absence of a gold standard characteristic or test for the diagnosis of neuropathic pain, it is important to examine common approaches to identify this

condition in order to choose a suitable method to use in assessing acute neuropathic pain.

2.2 Clinical features of neuropathic pain

Pain resulting from nerve injury or disease has distinct clinical characteristics that help to distinguish it from pain syndromes in which the nervous system remains unaltered (nociceptive pain). Broadly, these characteristics are commonly divided into positive and negative symptoms and signs. A key negative feature is pain arising in an area of sensory deficit. The sensory deficit arises as a result of damage to the peripheral or central somatosensory nervous system and may manifest itself for example as a reduced perception of noxious or heat stimuli. Some experts believe this in itself is the most important feature of neuropathic pain, while others stress the need for pain and sensory abnormalities to be linked to a neurological condition. Positive somatosensory features are also common, and include spontaneous and evoked symptoms and signs. Spontaneous pains occur without a stimulus and can be continuous or paroxysmal, the latter often being described as shooting or electric shock like in nature. Some patients describe paresthesias such as tingling or unpleasant sensations under the skin ('ants crawling'). Evoked pains occur as a result of a stimulus and are typically reported as an area of increased sensitivity to heat, cold or mechanical factors. Allodynia refers to pain evoked by a normally non-painful stimulus (such as lightly touching the skin). Hyperalgesia is an increased sensitivity to a normally painful stimulus. Hyperpathia is a further example of evoked pain, whereby a repetitive mildly painful stimulus results in progressive aggravation of pain symptoms.

It is important to note that not all patients with neuropathic pain will present with all the characteristics presented above. Similarly no single symptom or sign is absolutely diagnostic of neuropathic pain. However, the subjective pain experience, and the description of symptoms and signs used by patients is so distinct in neuropathic pain states that they have been examined as a method of aiding neuropathic pain diagnosis.

2.2.1 Verbal descriptors of neuropathic pain

In most languages, there are a multitude of adjectives available to describe a particular pain experience. Following the development of early pain questionnaires, in particular the McGill Pain Questionnaire, it became apparent that verbal descriptors used by patients might have diagnostic properties. In 1976, Dubuisson and Melzack demonstrated that patients with different types of pain described their symptoms using a distinctive constellation of adjectives.[186] Using the McGill Pain Questionnaire, they examined 95 patients with 8 different pain diagnoses, including two commonly considered to be neuropathic; phantom pain and post herpetic neuralgia. Their results showed a high degree of uniformity in the words used to describe particular pain conditions, and that the descriptors differed significantly between diagnoses, such that 77% of patients could be correctly classified into a specific pain syndrome solely on the basis of verbal description. For example, patients with phantom limb pain tended to describe their pain as 'throbbing', 'stabbing', 'sharp', 'cramping', 'burning' and 'aching'.[186] In contrast, those with arthritis described their pain as 'gnawing' and 'aching'.[186]

A subsequent study by Masson et al., (1989) also used the McGill Pain Questionnaire to examine the differences in verbal descriptors between a group

of patients with diabetic peripheral neuropathy and a second group with painful legs or feet of varying aetiologies.[187] They found significant differences between the neuropathic pain and control group, with discriminant analysis able to correctly classify 91% of patients according to their questionnaire response.

Boureau et al., (1990) also investigated the role of verbal descriptors, specifically examining their diagnostic properties in neuropathic pain.[188] Using a French reconstructed version of the McGill Pain Questionnaire, they compared verbal descriptors chosen by 100 patients with diagnosed neuropathic pain, with a control group of 100 patients with chronic benign pain. They demonstrated a significant difference in sensory descriptors between the two groups, with the six most commonly used adjectives amongst the neuropathic pain patients being: electric shock, burning, cold, pricking, tingling and itching. They conclude that 'verbal description is one more index that may lead the clinician to a correct diagnosis'.[188]

Mackey et al., (2012) developed a two factor model describing two groups of McGill Pain Questionnaire sensory descriptors that were common amongst patients with diabetic peripheral neuropathy and post herpetic neuralgia.[189] Factor 1 (dubbed 'stabbing pain') was characterized by the sensory descriptors stabbing, sharp and shooting. Factor 2 (dubbed 'heavy pain') included the descriptors heavy, gnawing and aching. They proposed these two common sets of descriptors reflected distinctive pain sensations common to neuropathic pain, but mediated by different mechanisms (such as $A\delta$ and C fibre pain transmission).[189]

However, not all studies of verbal descriptors in neuropathic pain agree with these results. Atkinson et al., (1982), using the same questionnaire, failed to demonstrate that pain descriptors had discriminant properties amongst a group of 126 chronic pain patients. They noted that the McGill Pain Questionnaire was unable to discriminate between underlying pain mechanism, including differentiating neuropathic from bone or visceral pain. They also commented that as affective disturbance increased, pain language become more diffuse.[190]

Similarly, in a study investigating verbal descriptors in three groups of patients with 'definite', 'possible' or 'unlikely' neuropathic pain, researchers found that pain descriptors (including the McGill Pain Questionnaire) could not distinguish between the three clinical categories, with considerable overlap between patients with definite or possible neuropathic pain, and those with unlikely neuropathic pain diagnoses.[191]

Nevertheless, there is some evidence that sensory and affective pain descriptors may predict response to particular analgesic medication. Gilron et al., (2013), as secondary analysis of data from a randomized control trial examining the effects or morphine and gabapentin in diabetic neuropathy and post herpetic neuralgia, discovered a differential effect of these drugs on pain descriptors.[192] For example, the severity of throbbing, shooting and aching pain improved preferentially with morphine, and tiring-exhausting and sickening pain with gabapentin.[192] Similarly, Carroll et al., (2010) found that pain descriptors predicted response to intravenous lidocaine pain treatment.[193]

The recognition that verbal descriptors may have discriminatory properties, and therefore provide an aid to diagnosing neuropathic pain led to the development

of a number of screening tools and neuropathic pain assessment scales. These tools arose through recognition that patients often presented with a mixed nociceptive/neuropathic picture (for example back pain and radicular leg pain) and that identifying a significant neuropathic component to their pain would have important implications for treatment.

2.2.2 Neuropathic pain screening tools

Since 2001, five neuropathic screening tools have been published and validated in the medical literature: The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS and S-LANSS [appendix 1 and 2]), The Douleur Neuropathique en 4 Questions (DN4 and DN4Interview), The Neuropathic Pain Questionnaire (NPQ), ID Pain and painDETECT.[36, 194-198] The common aim of these screening tools is to identify individuals who may have a significant neuropathic component to their pain experience. All the tools are different, however they are all based on pain description with or without the use of simple bedside sensory testing. Each screening questionnaire was developed in a broadly similar manner. An initial selection of items thought to be discriminatory was devised, based on published literature, questionnaires and expert opinion. A comparison was subsequently made of the frequency of descriptors used in neuropathic and non-neuropathic pain populations, with the aim of identifying the most discriminant items. These were then incorporated into a questionnaire that was validated in a second sample of pain patients, allowing an estimation of sensitivity and specificity based on a "gold standard" diagnosis.

Two of the screening tools, the LANSS and DN4 are administered by a clinician and include questions related to both pain quality and items of sensory examination.[194, 195] Versions of each tool have subsequently been validated as

self-administered questionnaires (S-LANSS and DN4 Interview). The remaining questionnaires, the ID Pain, NPQ and painDETECT are self-administered and contain only items related to the symptoms of neuropathic pain.

The majority of screening tools were validated in patients with peripheral neuropathic pain of mixed aetiologies, with the DN4 also including patients with central neuropathic pain.[195] The LANSS and ID Pain also included patients with complex regional pain syndrome type 1.[194, 198] The "gold standard" used to validate the questionnaires was diagnosis by a pain clinician, with some studies (DN4) requiring demonstrable nerve lesions.

Each questionnaire differs in the number and phraseology of questions used. The LANSS includes 5 questions phrased in a specific manner related to symptoms and 2 examination items, with each question receiving a different "weighting" in the total score. In contrast the DN4 has 7 symptom questions, and although these are more specific (each question asking about a specific descriptor rather than a group of related descriptors), the way in which the question is phrased to the patient is not specified, and the answers are not weighted differently. The NPQ has 10 items related to sensations and 2 further items related to affect, with responses rated on a visual analogue scale (VAS), similarly the painDETECT grades the response to 7 sensory descriptor items 0: hardly noticed to 5: very strongly, with a further 2 items related to spatial and temporal pain characteristics. The ID Pain comprises 6 items with dichotomous answers, and includes one item asking if the pain is limited to a particular joint. Both the DN4 and painDETECT were initially developed and validated in languages other than English (French and German respectively).

Understandably, the initial reported sensitivity and specificity of each tool differs, and these are presented in table 2.1. What is interesting however, is that despite differences in the development and validation of these tools there are a number of verbal descriptors identified by each process that are common across all tools. Items related to paraesthesias or dysaesthesias (pricking, tingling or pins and needles), electric shocks, hot or burning pain and items related to the symptoms/signs of allodynia and numbness are present across all 5 questionnaires suggesting these represent the core symptoms of neuropathic pain, and providing compelling evidence for the validity of using symptoms as diagnostic indicators.[185, 199] A number of these questionnaires have been validated in different languages, suggesting that pain qualities have a biological basis that is common despite different cultures. [185]

Screening Tool	Sensitivity (%)	Specificity (%)
LANSS	85	80
DN4	83	90
NPQ	66	74
painDETECT	85	80
ID-Pain	n/a	n/a

Table 2.1 Diagnostic sensitivity and specificity of the common neuropathic pain screening tools

LANSS = Leeds Assessment of Neuropathic Symptoms and Signs, DN4 = Douleur Neuropathique en 4 questions, NPQ = Neuropathic Pain Questionnaire.

It is important to note that screening tools fail to identify 10-20% of patients with clinician diagnosed neuropathic pain. The development of the tools involved an inevitable overlap of the symptoms included in the questionnaire and those

sought by the 'gold standard' clinician diagnosis by which they were compared, introducing a possible element of bias and inevitable questions about their validity. Nevertheless, tools that used demonstrable nerve lesions as part of the gold standard diagnostic process (DN4) show similar sensitivity and specificity to those that do not (LANSS).[194, 195]

The role of screening tools has been questioned in light of the recent change in definition and consensus statement on the grading of neuropathic pain, with emphasis placed on the need for diagnostic tests confirming a nerve lesion to label a patient with 'definite' neuropathic pain.[138] Nevertheless, screening tools are considered to play a role in the clinical and research arenas by a number of subsequently published international guidelines. The consensus of opinion from these publications seems to be that on an individual patient level, screening tools have a valuable role in allowing the non-specialist to identify a patient who may have neuropathic pain, which can steer the clinician towards confirming the diagnosis with a more in depth examination and investigations. [177-179]

Although screening tools are not replacements for clinical judgment in neuropathic pain diagnosis, their ease of use by both healthcare professionals (including non-specialists and nurses) and patients make them attractive for use in assessing neuropathic pain at a population level. One reported strength of screening tools is as a standardized case identification tool in epidemiological studies, particularly as they are suited to use face to face, via telephone, post or internet.[199] However, guidelines on the assessment of neuropathic pain do indicate there is a lack of validation studies for use of screening tools in this context.[179] Nevertheless, two separate epidemiological studies using different screening tools, in different European countries demonstrated remarkably

similar results when estimating the prevalence of neuropathic pain in the general population. Torrance et al., (2006) in a survey of 6000 members of the general public using the S-LANSS questionnaire reported a prevalence of pain with neuropathic characteristics of 8.2%.[42] In a subsequent French study of 30000 people using the DN4 interview, the reported prevalence of neuropathic pain characteristics was 6.9%.[43] Although screening tools were not validated for use in this manner, the similarity in results would suggest they may be reliable to use in epidemiological studies.[185] Screening tools have also been used to estimate the prevalence of neuropathic pain characteristics in a number of specific disease conditions including diabetes, back pain and Parkinson's disease.[36, 200, 201]

During the research presented in this thesis the definition of neuropathic pain has changed, and a system of grading neuropathic pain diagnosis has been introduced in order to bring clarity to research in this area. However, a number of issues remain unchanged: there remains no gold standard for diagnosing neuropathic pain, and there are a number of practical difficulties in using a more traditional approach where neurological signs are considered more important than pain descriptors. From the evidence presented, verbal descriptors do seem to have diagnostic qualities in distinguishing neuropathic from nociceptive pain, and the subsequent development of screening tools based on this observation has provided a useful research tool. Screening tools seem particularly useful in estimating the prevalence of neuropathic pain characteristics in population based studies, and represent a reproducible and standardized method of assessment, in a field where the diagnostic goal posts have shifted significantly in the last five years.

Throughout this thesis one such screening tool, the LANSS and it's self report version the S-LANSS are used to assess neuropathic pain characteristics in the post surgical population, therefore it is useful to consider this tool in more detail.

2.3 The LANSS and S-LANSS screening tools

The LANSS was the first screening tool to be developed with the aim of distinguishing neuropathic from nociceptive pain. It was developed by a two-stage process involving the initial step of identifying discriminatory factors and building a questionnaire, followed by a second study testing the scale on patients.

The first stage in the development of the questionnaire was identifying six groups of symptoms thought to be of discriminatory value by reviewing published research and expert opinion in this area. The six symptom groups represented continuous deep pain, paroxysmal pain, evoked pain, autonomic dysfunction, thermal pain quality and dysaesthesias. In contrast to subsequently developed screening tools (such as the DN4), questions were constructed to reflect the essence of these symptom groups and therefore contained more than 1 descriptor. Questions were thought to be a more sensitive way of obtaining sensory information compared with the use of descriptors alone. The inclusion of an autonomic dysfunction group (and the subsequent use of CRPS patients in the study) could perhaps be considered a confounding factor in light of the recent neuropathic pain definition change, however the exclusion of CRPS as a neuropathic pain entity by IASP could at best be described as controversial, with much opinion still regarding CRPS as a neuropathic pain process.

In addition to verbal descriptor groups, limited bedside sensory testing was also identified as a possible discriminatory factor, and included in the initial phase of study design in the form of testing for allodynia using cotton wool and pin-prick testing for hyperalgesia or hypoalgesia.

Once the groups of descriptors and sensory testing were identified, 30 neuropathic pain patients and 30 nociceptive pain patients were recruited to assess the presence of these factors. The neuropathic pain group comprised a number of neuropathic pain diagnoses including post-surgical, peripheral neuropathy, post herpetic neuralgia and phantom limb pain. In contrast, the nociceptive group comprised predominantly those with low back pain and arthropathies, a fact criticized in subsequent comment on the LANSS scale development, with concerns that low back pain often has a mixed pain picture that may have confounded the tool development. However, the diagnostic groups used in this stage of the LANSS development were rigorously assessed by chronic pain experts, using history, examination and available imaging and neurophysiological testing, an approach still deemed the gold standard in diagnosing neuropathic pain.

Each of the 60 patients was asked to rate whether the descriptors described their pain (with a yes/no response). Non-parametric testing revealed a number of descriptors significantly associated with neuropathic pain across the five symptoms categories identified in the prior literature search, and also in the results of the examination testing with light touch and pin-prick. The one group of pain symptoms, which had a similar distribution across both groups, was related to 'continuous deep pain'. This group of symptoms was not included in the final scale design.

Logistic regression modeling was then used to identify the combination of items that would best predict the presence of neuropathic pain. The co-efficient resulting from this method reflected the odds ratio of a person with neuropathic pain answering positively for a given item, and this information was used in the final scale design to give a weighting to each question, reflecting the contribution of that item to an overall diagnosis of neuropathic pain within the model. For example, the odds ratio for the dysaesthesia group of symptoms was 5.24, hence in the final scale the question related to this group of symptoms was given a weighting of 5 if answered positively. Using this approach, the final scale has a maximum score of 24. A cut off point of 12 was identified as having the optimum positive and negative predictive values (83% sensitivity and 87% specificity). In applying the scale retrospectively to the responses from the 60 initial patients, the median score in the neuropathic group was 17, and in the nociceptive group 4. Interestingly, 4 patients in the nociceptive group were misclassified as neuropathic. All these patients had sensory dysfunction in the area of pain (although none had allodynia). Sensory dysfunction in the nociceptive group led one commentator to question whether these patients actually had neuropathic pain, and to question the underlying diagnosis and therefore the basis for the scale construction.[202] This was refuted in further commentary suggesting that altered sensory perception in nociceptive pain of musculoskeletal origin is not unusual, and to suggest this must be neuropathic is "nonsense".[203]

Once the LANSS scale was constructed, a further 20 neuropathic and 20 nociceptive pain patients were recruited to examine the validity and reliability. Each patient received the screening questionnaire twice, by both the

investigator and also an independent clinician in order to examine inter-rater agreement. In this cohort, the LANSS reported 85% sensitivity and 80% specificity, with good internal consistency between items and good agreement between the ratings of the investigator and clinician. Cronbach's alpha was 0.74.

One criticism of the LANSS was the exclusive use of neuropathic pain patients with peripheral nerve injury to develop and validate the tool, with concerns that the performance of the tool in identifying patients with central neuropathic pain (such as post-stroke pain or spinal cord injury) may be impaired.[202] Nevertheless, subsequent publications recommended the LANSS for use in this context, and other authors describe cohorts of spinal cord injury patients with neuropathic pain and confirmatory high LANSS scores.[204, 205] However, in a Swedish study examining the accuracy of screening tools in this population, the LANSS did not perform as well as the original validation study (sensitivity 35.7%, specificity 100%, agreement 55%).[206]

The LANSS has been tested and validated in a number of other settings, including diverse diseases, cultural and language groups. The LANSS has been translated into Spanish, with a sensitivity of 91% and specificity of 89%.[207] Similarly, Turkish versions of the LANSS returned sensitivity of 70-90% and specificity of 94-97%.[208, 209] An Ethiopian version returned sensitivity of 85% and specificity of 42% (although the results may be influenced by the study population, which entirely comprised patients with leprosy).[210] A Chinese version of the LANSS returned 80% sensitivity and 97% specificity.[211] In a population with head and neck cancer, Potter et al., showed a sensitivity of 79% and a specificity of 100%.[212] The LANSS has been used to estimate the

prevalence of neuropathic pain in a variety of conditions including back pain, Parkinson's disease, trauma, musculoskeletal pain, and leg ulcers.[162, 201, 213-216] The relative consistency in diagnostic accuracy across several settings suggests the initial validation study of the LANSS is likely to represent an accurate reflection of sensitivity and specificity, especially if examining patients who are likely to have peripheral neuropathic pain.

The LANSS pain scale has subsequently been modified into a self-report version, dubbed the S-LANSS.[196] The use of examination items (pin prick, and light touch) and the intention for the screening tools to be healthcare worker administered hampered the use of the LANSS for large scale epidemiological research both in the clinical setting and also by survey. The S-LANSS (appendix 2) was designed to overcome this problem by removing the need for clinical examination and by ensuring the patients could complete it themselves.

Of the 5 original symptom questions from the LANSS, only question 4 (related to symptoms of electric shocks and spontaneous pain) remained unchanged. The other 4 questions underwent subtle alterations in the S-LANSS version, although the essence of the questions remained the same, with the same symptoms groupings as the original LANSS. The 2 LANSS examination items were altered to prompt the patient to examine the painful area themselves (with a finger), attempting to elicit allodynia and/or hyper or hypoalgesia in common with the original LANSS questions. Scoring and cut off points for the diagnosis of neuropathic pain in the S-LANSS remained identical to the LANSS. A body map, to indicate pain site and a 0-11 numerical rating scale of pain intensity were added.

The new scale was initially validated in both a clinic setting, and then in a postal validation study. In the clinical validation study, 200 patients were diagnosed with either neuropathic (n=100) or nociceptive (n=100) pain by an experienced pain physician using history, examination and investigations. The patients then completed the S-LANSS unaided and also by interview. The sensitivity and specificity of the unaided S-LANSS was 74% and 76% respectively, and the S-LANSS completed by interview 74% and 83%. Cronbach's alpha was 0.76 and 0.81 for the self completed and interview completed scores. The validity of the S-LANSS was further confirmed by comparison with the NPS, and examining the relationship between each S-LANSS item and the total score/clinical diagnosis

The S-LANSS was also validated in a postal survey setting against a proxy gold standard of a simultaneously completed NPS. A mixture of general practice and pain clinic patients returned 174 completed surveys, and the S-LANSS demonstrated to perform in a similar way to the clinic validation study when compared to the NPS. Cronbach's alpha for the postal survey group was 0.8.

Like the LANSS, the S-LANSS failed to correctly classify 20-25% of patients, an important limitation for a screening tool aimed at gathering epidemiological data. The reliance on a gold standard comparator of diagnosis by an experienced pain clinician potentially adds further diagnostic variance and therefore influences the validity of the scale, although at the time of development there was an absence of consistent, clear and testable definitions of neuropathic pain. To compound this problem, postal survey results were themselves compared to a tool not validated as a screening tool for neuropathic pain (the NPS).

The potential variability in the gold standard comparator for the S-LANSS has been cited as one possible reason why subsequent studies have demonstrated lower sensitivity and specificity than the original validation cohort. In a study of community-based patients in North America, Weingarten et al., (2007) compared a postal, self-completed S-LANSS and telephone interview S-LANSS with clinical assessment.[217] The sensitivity and specificity for the self-completed S-LANSS was 57% and 69% respectively, and for the interview S-LANSS 52% and 78%. Both values are significantly less than the initial S-LANSS validation study. The authors demonstrated that the self-examination items, to test for altered sensation, only demonstrated modest agreement with clinical examination (sensitivity 61-80% and specificity 58-71% depending on the item and method of applying the questionnaire).[217] In addition, the calculated odds ratios for each item, from which the item weighting was derived, differed from the original LANSS odds ratios that were used in the questionnaire development.

Although the results of this study question the validity of using the S-LANSS as an epidemiological tool to assess the prevalence of neuropathic disorders, the study was not without potential confounding factors. Firstly, a number of patients deemed to have neuropathic pain by clinical assessment also had significant nociceptive pain. Patients were assigned to the neuropathic pain group if any of their pain component was neuropathic, so some patients may have had sensory disturbance suggestive of neuropathic pain but overriding nociceptive pain experience and verbal descriptors. The S-LANSS would tend towards classifying these patients as having predominantly nociceptive pain, whereas in the study having even a minor contribution of neuropathic pain in

the overall pain experience would lead them to be classified in the neuropathic category at clinical examination. Clearly, this would adversely affect the sensitivity and specificity of the questionnaire. A further confounding factor was the length of time taken between assessment methods. The delay between mailed questionnaire and clinical assessment was 15 months, during which symptoms and signs may have changed significantly, indeed 10 subjects had resolution of their pain completely by the time of their clinical assessment. Such factors may explain the differences between the reported sensitivity and specificity in this study and both the original validation study and further validation performed on a Turkish version of the questionnaire, which reported similar sensitivity (72%) and specificity (80%) to the original results.[218]

The validity of the S-LANSS has been further examined by comparison with other screening tools and measures of neuropathic pain. In a cohort of breast cancer survivors, the total ID Pain score was significantly associated with the total S-LANSS score (r=0.54, P <0.001).[219] Similarly, there was a moderate to high correlation between total scores in a modified painDetect questionnaire and the S-LANSS in osteoarthritis patients (r=0.73, P<0.0001).[220] Lastly, in an observational study of patients with radicular leg pain, the S-LANSS was compared with the DN4, with again moderate to good correlation in total scores (r=0.62, P,0.001), although only fair agreement on neuropathic pain diagnosis suggesting incongruent cut off points.[221] Two independent studies using the S-LANSS and DN4 interview to estimate the prevalence of neuropathic pain in the general population in the UK and France respectively provided remarkably similar estimates (8.2% and 6.9%), adding to the argument for the validity of these tools.[42, 43]

One advantage of the S-LANSS was the high completion rates (95-99% for each question in the original validation study), supporting the acceptability of the questionnaire in postal research. Indeed the S-LANSS has been used extensively in investigating the prevalence of neuropathic pain in a number of diverse conditions including: pelvic pain, sarcoma, metastatic bone disease, dental surgery, ischaemic pain and the general population.[42, 222-227]

A further attribute of the S-LANSS is the correlation of the total score with clinician certainty of a neuropathic pain component in a mixed picture of pain.[228] Clinical scenarios rarely produce pain of 'pure' nociceptive or neuropathic pain, rather they are often a mixed picture (such as the diabetic with peripheral neuropathy and ulcers, or the back pain patient with radicular leg symptoms). This has led to the suggestion that pain can be more or less neuropathic, a construct supported by a study comparing S-LANSS scores with clinical certainty of a neuropathic component being unlikely, possible or definite.[228]

If screening tools such as the S-LANSS support the concept that pain can be more or less neuropathic, the natural suggestion would be to question whether or not screening tools are sensitive to changes in the degree of neuropathic pain a patient may experience with treatment. Indeed, a number of clinical trials have used the LANSS screening tool as an outcome measure, and have demonstrated corresponding reductions in LANSS and pain intensity scores in treatment groups compared to controls.[229-233]

The LANSS based screening tools offer a number of potential attributes to examining the prevalence of acute neuropathic pain in the post-surgical population. However, although these screening tools have been validated in

chronic pain patients, their modern psychometric properties have not been fully examined. The use of the LANSS as an outcome measure, although appears to have some face validity, has not been formally assessed. The fact that the LANSS has been used in this way, despite being designed as a screening tool, suggests a need for an outcome tool that reflects not simply change in pain intensity, but also change in neuropathic pain in response to treatment.

Pain is not directly measurable unlike many attributes in the physical sciences (for example length or weight). When a property is directly measureable, such as length, devising a measurement tool is relatively straightforward. The meter can be used to measure any structure, and remains unaffected by the item it is measuring, i.e. the interval between scale points on the meter does not vary with the item measured, thus the meter is an interval level measurement tool. In contrast, pain is a 'latent trait' that cannot be measured directly, and is normally assessed by the use of ordinal scales. The LANSS and the VAS would be examples of an ordinal scale; pain scores can be ranked but the distance between each point on the scale does not necessarily reflect equidistant steps in the underlying trait.[234] Furthermore, the level of pain required to reach a particular step on the scale may vary between subjects.

Ordinal scales are useful to determine if a patient has improved or worsened with treatment, and can separate patients into groups based on the magnitude of pain, and data from ordinal scales can be subjected to non-parametric statistics to aid interpretation of results. However, the type of analysis common to medical outcome studies often involves calculation of change scores, % improvement, effect sizes and minimum clinically important difference. Strictly speaking, this requires interval level scales that are capable of parametric

analysis.[235] Ordinal scales on the other hand do not support the mathematical operations needed to calculate means and standard deviations.[236]

Modern psychometric approaches to scale design and analysis are able to create interval level measurement of underlying latent traits, based on the theory that the important indication of a measurement structure is in the relationship between variables, not the physical values themselves. The practical realization of this theory of conjoint mechanism takes the form of Rasch analysis. Rasch analysis is the testing of a scale against a mathematical model that formalizes the axioms of conjoint measurement, and is capable of transforming ordinal scales into interval level measurement providing the data fit the Rasch model to an acceptable degree.[237]

For example, a neuropathic pain scale that satisfied the expectations of the Rasch model could be used to calculate the effect of treatment on an interval scale. This would have important implications for research and clinical practice.

The LANSS was developed as a neuropathic pain screening tool, however it may have properties that allow it to discriminate the magnitude of neuropathic pain experienced by a patient, and it appears to demonstrate change in relation to neuropathic pain treatment. No existing neuropathic pain tools have been developed to Rasch model standards, such that they can be used as interval level measurement tools. In order to explore this gap in knowledge about the properties of the LANSS tool, which may have implications for the way the tool can be used, and the statistics applied to data collected using it, the LANSS was investigated to see if it could satisfy Rasch model expectations and be transformed into an interval level measurement scale both in a general pain

population and more specifically in a cohort of patients with chronic
postoperative pain.

2.4 Methods

This study used data collected by a group of researchers in Belgium who
performed a multicentre observational survey on 2480 pain patients with the
aim of examining how neuropathic pain conditions are diagnosed and managed
in daily practice.[238] As part of this study, 177 general practitioners and 97
specialists were asked to complete a LANSS questionnaire on consecutive
patients presenting with chronic pain (>3 months duration) of any cause. Data
on the possible underlying cause of pain, and demographic details were also
recorded as part of the study. Clinicians were able to choose more than one
diagnostic category if more than one pain generator were present, or there was
diagnostic uncertainty. The frequency of different underlying diagnostic groups
is presented in table 2.2.

The Belgian study was supported by the pharmaceutical company Pfizer who
kindly granted full access to the original data. LANSS data from this study were
formatted in SPSS prior to exporting as an ASCII file to RUMM2020 Rasch
analysis software (RUMM Laboratory Pty Ltd.) for analysis. Rasch analysis was
performed on both a random representative sample of all LANSS patients
(n=400), and analysis of individual underlying disease diagnoses where the
number available for analysis was greater than 150 (following exclusion of
extreme scores). These groups comprised postsurgical pain, diabetic
neuropathy, osteoarthritis, post-traumatic injury and low back pain.

Rasch analysis of the LANSS data included a number of investigations

including fit to the Rasch model, scale reliability, scale multi-dimensionality and

differential item functioning.

Diagnosis	Number of patients
Diabetic neuropathy	253
Cancer	75
Low back pain	781
Osteoporosis	184
Multiple Sclerosis	38
Thalamic syndrome	11
Post-herpetic neuralgia	163
Post traumatic injury	326
CRPS	178
Alcohol abuse	85
Syringomyelia	11
Other	499
Post-surgical lesion	232
Carpal tunnel	91
Osteoarthritis	590
Post CVA	76

Table 2.2 Frequency of underlying causes for chronic pain recorded by Hans et al., (2007) and used in the Rasch analysis of LANSS data.

CRPS = Complex Regional Pain Syndrome, CVA = cerebrovascular accident

2.4.1 Fit to the Rasch Model

Each LANSS question has only two response options (yes or no), therefore the

dichotomous Rasch model was chosen to compare the difference between the

observed responses (from the LANSS data) and those expected by the Rasch

mathematical model. These differences, termed fit statistics are based on chi-

square calculations. RUMM2020 chi-square statistics compare the difference in observed and expected values across groups with different ability levels ('ability' in the case of the LANSS refers to different levels of neuropathic pain).[237] For a given LANSS question, a number of chi-square values are calculated across ability groups, and then summed to give an overall statistic for that item.[237] Residual statistics describe the standardized sum of all differences between observed and expected values summed over all persons.[237] Invariance across the trait is examined using a sum of the individual item chi-square values. This is termed the item-trait interaction fit statistic.[237] The data are also examined for aberrant response patterns from individuals, which may raise questions about the construct validity of the scale in a particular population. This analysis is termed person fit statistics, and is reported as a residual in a similar manner to item fit.

With perfect fit to the Rasch model, item and person residuals would have a mean of 0 and a standard deviation of 1. The chi-square item-trait interaction should be non-significant. For each individual item, fit residuals should lie between +/- 2.5 and chi-square results should be non-significant.

2.4.2 Scale Reliability

RUMM2020 reports a statistic termed the person separation index. This is an estimate of the internal consistency reliability of the scale, and as such indicates the power of the scale to discriminate among respondents. This statistic is analogous to Cronbach's alpha (using the calculated logit value instead of the raw score). The interpretation of the person separation index is the same as Cronbach's alpha, with a value of 0.7 regarded as the minimum acceptable to differentiate between two groups, and 0.9 to allow use on an individual level.[239]

2.4.3 Scale Multi-Dimensionality

The LANSS was examined to ensure that the scale is measuring only one latent construct (in this case, assumed to be neuropathic pain). This was by two methods, firstly through a confirmatory factor analysis based upon a tetrachoric correlation, and secondly via a method recommended by Smith (2002) for use within Rasch analysis.[240]

Confirmatory factor analysis was used initially to test the construct validity of the scale, as with only seven LANSS questions, principal component analysis of the residuals is likely to be underpowered. The latter test is based on the assumption that once the Rasch factor has been removed, there should be no relationship (other than random ones) between the LANSS questions. The test recommended by Smith (2002) involves using t-tests to compare person-locations based on different subsets of items located on the same scale.[240] If less than 5% of the t-test comparisons are significant, the scale is considered unidimensional.

2.4.4 Differential Item Functioning (DIF)

A key aspect of a measurement scale is invariance across different populations being measured. Differential Item Functioning occurs when different groups within a sample have a tendency to respond to scale questions in a different manner, for example, if women answered questions on the LANSS scale very differently to men, or younger persons answered differently to older persons. For the LANSS to demonstrate measurement properties, the response to a question should only depend on the level of neuropathic pain, irrespective of gender or age group. The LANSS was tested for DIF within RUMM2020 across gender and three age groups (0-35, 36-70, 71-99).

2.5 Results

2.5.1 Unidimensionality and Fit to the Rasch Model

Confirmatory factor analysis (CFA) on a random sample of 400 cases was performed by Professor Tennant, co-author of a research paper based on this work.[241] CFA indicated a strong unidimensional construct with a Root Mean Square Error of Approximation of 0.00; Comparative fit index (CFI) and Tucker-Lewis index (TLI) of 1.0.

Data were then analyzed for fit to the Rasch model. Both the random sample of 400 cases across diagnostic categories was analyzed, and also individual diagnostic categories with >150 respondents. Individuals with extreme scores (representing the maximum and minimum score on the LANSS scale) were excluded from the analysis (as there is no variation in their responses), hence the final number used in the calculation differs from the original number of respondents in that diagnostic category.

Summary Rasch statistics are presented in table 2.3. The Person Separation Index was 0.7 across all groups, indicating the scale has reliability consistent with use at the group level. Only two diagnostic categories, diabetic neuropathy and chronic post-surgical pain demonstrated acceptable fit to the Rasch model (demonstrated by non-significant Chi-square interaction statistics). Data from these two groups were further examined for unidimensionality, DIF and local dependency.

Table 2.3 Summary Rasch statistics for LANSS data collected by Hans et al., (2007), and presented according to underlying cause of pain

n = number of patients completing LANSS questionnaire, SD= standard deviation, df = degrees of freedom, PSI = person separation index

Analysis name	n	Item residual		Person residual		Chi-square interaction		PSI
		Value	SD	Value	SD	Value (df)	P	
Random sample	313	-0.071	1.54	-0.125	0.720	34	0.00	0.7
Osteoarthritis	386	0.053	1.103	-0.1	0.707	28	0.00	0.7
Post-surgical pain	173	0.222	1.245	-0.025	0.718	21	0.06	0.7
Trauma	213	0.109	1.427	-0.029	0.7	21	0.00	0.8
Diabetic neuropathy	171	-0.213	1.065	-0.146	0.743	28	0.05	0.7
Low back pain	558	-0.05	1.495	-0.112	0.684	28	0.00	0.7

Further tests of unidimensionality were performed in the two groups that fit the

Rasch model to an acceptable degree. Independent t-tests were used to

compare person locations that had been estimated using two different subsets

of items from the final scale. The three highest positive loading items on the first

residual component were compared with the four highest negative loading items

(with both sets calibrated on the same metric scale). For the diabetic

neuropathy population, 170 t-test comparisons were made, and 173

comparisons in the post-surgical pain group. None of these were significant,

further supporting the unidimensionality of the scale in this group.

2.5.2 Differential Item Functioning (DIF)

No LANSS questions demonstrated evidence of uniform or non-uniform DIF

(following Bonferroni adjustment) between gender or age groups, in both the

diabetic neuropathy and post-surgical pain cohorts. The LANSS scale items are

measuring the same construct across these person factors.

2.5.3 Local Dependency

Local dependency occurs when an individual's response to one question on the

scale will influence their response to another different question on the scale.

RUMM2020 searches for positive correlations among item residuals, to

determine if local dependency exists. For the LANSS groups, no question had

correlations greater than 0.3 in both groups analyzed, indicating an absence of

local dependency.

2.5.4 Item-Person Threshold Distributions

As the diabetic neuropathy and post-surgical pain groups of LANSS data fit the

Rasch model to an acceptable degree, it was possible to create a distribution

map comparing LANSS question difficulty with distributions of person 'ability' on the same logit scale. These are termed item-person threshold distribution maps and are presented in figures 2.1 and 2.2 for diabetic neuropathy and post-surgical pain respectively. In both groups the item difficulties are spread through the middle of the ability range, with some evidence of a floor and ceiling effect (meaning the scale is less discriminating at lower and higher levels of neuropathic pain).

The raw scores for the LANSS scale were transformed into interval scale scores and are presented in table 2.4.

	Interval score (logits)	
LANSS raw score	Diabetic neuropathy	Post-surgical pain
0	-2.66	-2.56
1	-1.73	-1.64
2	-0.98	-0.92
3	-0.36	-0.32
4	0.23	0.25
5	0.90	0.87
6	1.78	1.67
7	2.88	2.68

Table 2.4 Rasch transformed interval scale scores (in logits) for diabetic neuropathy and post-surgical pain patients.

LANSS = Leeds Assessment of Neuropathic Symptoms and Signs
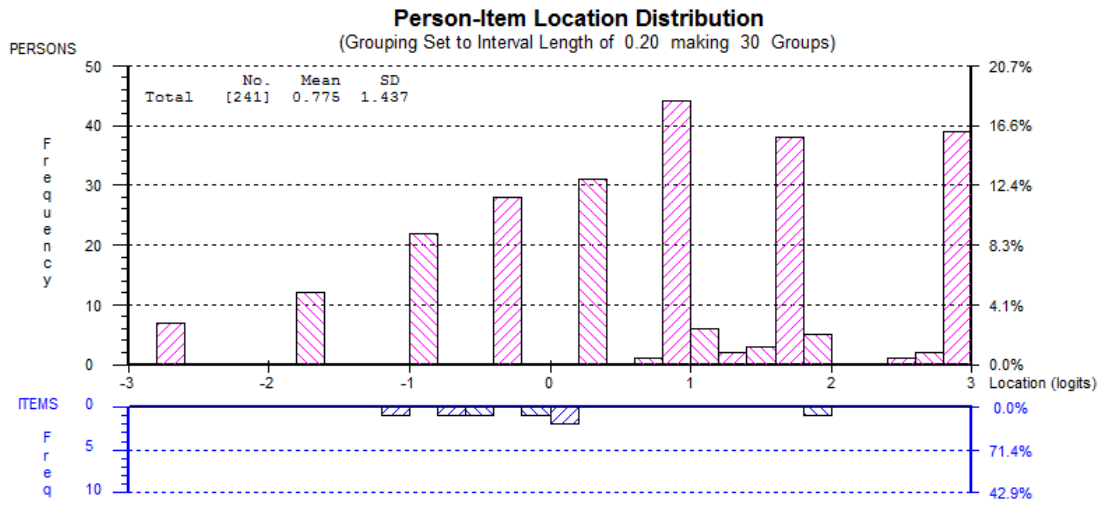
Figure 2.1 Rasch analysis item person threshold map for diabetic neuropathy pain patients.
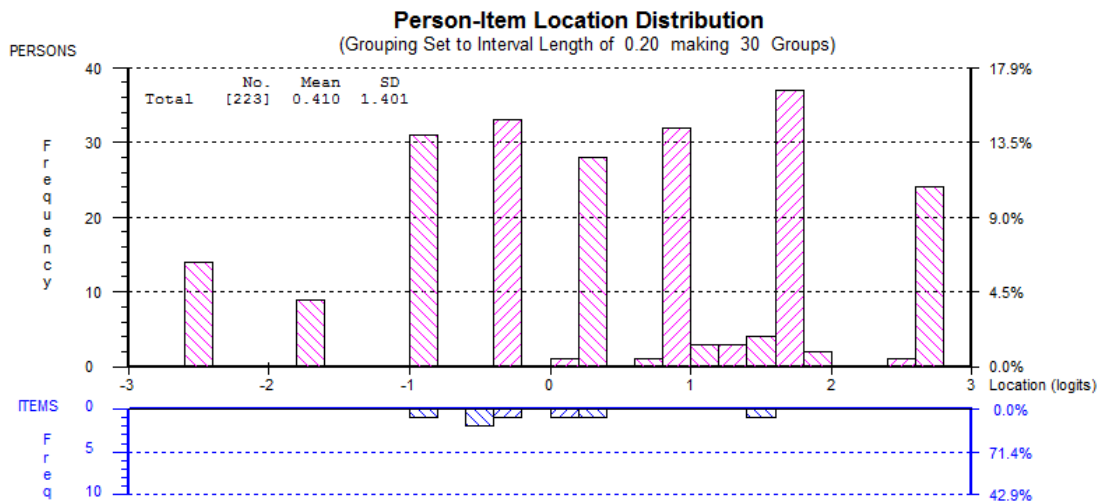
Figure 2.2 Rasch analysis item person threshold map for Post-surgical pain patients

2.6 Discussion

Item response theory, and in particular Rasch analysis is being increasingly used to develop and evaluate outcome measures within medicine. No previous study has sought to investigate the modern psychometric measurement properties of a neuropathic pain screening tool such as the LANSS using item response theory or Rasch analysis. This is an important gap in knowledge, as this scale has already been used as an outcome measure in published studies. Although the LANSS based scales seem to be able to differentiate pain that is more or less neuropathic, and show response to treatment effect, they were not designed to be used in this way and have not been formally validated in this context. Rasch analysis provides a way of assessing the validity of using the LANSS as a measurement tool.

Analysis of the LANSS data shows that for patients with diabetic neuropathy and chronic post-surgical pain, the LANSS fits the Rasch measurement model to an acceptable degree. The scale measures a single construct (neuropathic pain), and does not vary across gender or age group. LANSS raw scores could therefore be transformed into interval level measurement for these groups.

There are a number of limitations to this interpretation. Importantly, the reliability of the LANSS only allows statistical interpretation at the group level, and cannot be reliably used to measure change in individuals. The LANSS has a relatively low number of questions for a measurement scale (7), and this is likely to contribute to its poor discriminatory properties at either end of the neuropathic pain spectrum. Classical tests of reliability are not well suited to non-normal distributions found in population screening tools, where the emphasis is on a cut point, not the fact that large numbers of people are well below this

level.[242]Screening tools need the test information function to be maximized at the cut point, which explains the poor levels of precision (when transformed to an interval measure) at the margins of the scale.

Neither should the LANSS be used as a generalized measurement tool across pain diagnostic groups, and the analysis shows the LANSS does not fit the Rasch model to an acceptable degree when used across all pain diagnostic categories. This may reflect the fact that the analysis included pain diagnoses that are more associated with nociceptive pain (such as osteoarthritis and low back pain). Assuming the construct the LANSS is measuring is neuropathic pain, it is not surprising that it failed to demonstrate measurement properties in these groups. In contrast diabetic neuropathy is regarded as neuropathic pain, and the LANSS shows measurement properties in this group. The fact that the LANSS also demonstrates measurement properties in patients with chronic post-surgical pain lends further weight to the hypothesis that this condition is commonly a neuropathic pain state.

To date, only one other scale assessing the quality of pain has been assessed with item response theory. The Pain Quality Assessment Scale (PQAS) is a revised version of the Neuropathic Pain Scale (NPS), to which were added questions to allow assessment of non-neuropathic pain.[243] Although this scale was designed as a measurement tool across pain categories, it demonstrated a number of issues when examined with item response theory. These included variability in the precision of the subscales and a lack of interval scaling/redundant items for the 0 to 10 response levels.[244]

Despite its weaknesses, the LANSS therefore is the only neuropathic pain tool to have demonstrated neuropathic pain measurement properties in a cohort of patients with chronic post-surgical pain. The psychometric properties of the LANSS elicited by the Rasch analysis lend support to its use to further assess neuropathic pain following surgery, during the immediate post-operative period.

3 The prevalence of acute & chronic neuropathic pain following thoracic surgery

3.1 Introduction

From the evidence presented in Chapter 1, there are basic science and clinical reasons to suggest that a proportion of postoperative patients experience a significant neuropathic component to their acute pain experience. The epidemiology of this acute postoperative neuropathic pain is poorly described, with only one prospective audit published on the topic.[174] This study had a number of potential methodological flaws including a failure to exclude patients with pre-existing neuropathic pain, only evaluating patients with poorly controlled pain and a failure to use a validated method of neuropathic pain assessment.

It was hypothesized that some patients experience a significant neuropathic component to their acute post surgical pain experience, and that these patients would be at risk of developing chronic neuropathic pain following surgery. The research presented in this chapter aims to estimate the prevalence of acute neuropathic pain following thoracic surgery, and also whether acute neuropathic pain is associated with the development of chronic neuropathic pain 3 months later.

Patients undergoing thoracic surgery were chosen as the study population. Chronic pain following thoracic surgery is widely reported as a common complication; the prevalence is often reported as >50% (table 3.1).

Reference	N=	Surgical approach	Chronic pain time point	Chronic pain prevalence
Dajczman et al., (1991)[245]	56	T	20 months*	54%
Kalso et al., (1992)[246]	134	-	30 months*	44%
Richardson et al., (1994)[247]	883	T	2 months	22%
Richardson et al., (1994)[247]	883	T	12 months	14%
Landreneau et al., (1994)[146]	142	V	3-12 months	30%
Landreneau et al., (1994)[146]	36	V	13-31 months	22%
Landreneau et al., (1994)[146]	97	T	3-12 months	44%
Landreneau et al., (1994)[146]	68	T	13-31 months	29%
Bertrand et al., (1996)[248]	146	V	25 months	63%[#]
Bertrand et al., (1996)[248]	87	T	33 months	61%[#]
Katz et al., (1996)[167]	23	T	18 months	52%
Perttunen et al., (1999)[249]	62	T	12 months	61%
Obata et al., (1999)[250]	28	T	3 months	50%
Obata et al., (1999)[250]	30	T	3 months	77%
Obata et al., (1999)[250]	28	T	6 months	33%
Obata et al., (1999)[250]	30	T	6 months	67%
Passlick et al., (2001)[251]	60	V	59 months*	32%
Gotoda et al., (2001)[137]	85	T	12 months	41%
Ochroch et al., (2005)[252]	120	T	3 & 4 months	45%
Ochroch et al., (2005)[252]	120	T	6 months	35%
Ochroch et al., (2005)[252]	120	T	9 & 12 months	21%
Maguire et al., (2006)[253]	482	T	7 months-7years	45%
Maguire et al., (2006)[253]	118	V	7 months-7years	41%
Maguire et al., (2006)[253]	31	T	3 months	52%
Pluijms et al., (2006)[254]	149	T	6-42 months	52%
Steegers et al., (2008)[255]	144	T	23 months*	40%
Steegers et al., (2008)[255]	60	V	23 months*	47%

Table 3.1 The reported prevalence of chronic post thoracic surgery pain

V=Video Assisted Thoracoscopic Surgery, T=Thoracotomy, N = number of patients examined

Of these patients with chronic pain, 52-66% will have a neuropathic pain component.[135]

The chest wall is richly innervated with nerve supply, and a number of studies have demonstrated objective evidence of nerve damage following both thoracotomy and also video assisted thoracic surgery (VATS) procedures.[64-66] Signs of nerve damage seem to be associated with more severe acute pain following thoracic surgery.[64] In turn, the severity of acute pain seems to predict the development of chronic pain after thoracic surgery.[167]

With a relatively high prevalence of chronic neuropathic pain and well described mechanisms of nerve injury at the time of surgery, thoracic surgery patients would appear to be an ideal population to explore the existence of acute postoperative neuropathic pain.

The proportion of patients experiencing acute neuropathic pain in the thoracic surgery population is not known. Although acute pain intensity following thoracic surgery is associated with the development of chronic pain, it is not known if pain character predicts the development of chronic neuropathic pain in this population.

The aim of this study was to determine the incidence of acute and chronic neuropathic pain following thoracic surgery. It was hypothesized that the occurrence of acute neuropathic pain characteristics following thoracic surgery would be associated with significantly higher odds of developing chronic neuropathic pain characteristics 3 months later.

3.2 Methods

3.2.1 Study design

The study was designed as a prospective, observational cohort study. After ethics committee approval, adult patients admitted to St James's University Hospital (Leeds, UK) for VATS or thoracotomy were recruited. Patients were excluded if they had previously undergone VATS or thoracotomy, had previously diagnosed neuropathic pain or were pregnant.

The primary aim was to assess the proportion of patients who experienced acute neuropathic pain characteristics following thoracic surgery. The secondary aim was to investigate the incidence of chronic neuropathic pain in this cohort 3 months after surgery, and to explore possible links between the two.

Following a review of neuropathic pain assessment tools (outlined in chapter 2), the LANSS and S-LANSS neuropathic pain screening tools were chosen. We used screening tools rather than clinician assessment alone, to ensure consistency and reduce missing data between assessments in the acute and follow up periods. In addition, the validity of using the LANSS based screening tools in the post-surgical neuropathic pain population was enhanced by the Rasch analysis presented in Chapter 2, which demonstrated the tool had some measurement properties in this population.

Following informed consent, a medical researcher performed a baseline pre-operative LANSS score on the day before scheduled surgery (performing the examination items at the expected site of surgery). Patients who had positive LANSS scores at this stage were withdrawn from the study. Patient

demographics and the operation performed were recorded. During the post-operative period the medical researcher repeated the LANSS score whilst the patient was in hospital. This examination was conducted at least 24 hours after regional or local anaesthetic infusion or injection had ceased. Three months following their operation, patients were sent an S-LANSS questionnaire by post. This self-report version of the LANSS score included a numerical rating scale (anchored 0: no pain and 10: severe pain) recording pain intensity. Those failing to return the postal questionnaire were telephoned after a further two weeks and where possible the S-LANSS was completed by telephone interview.

3.2.2 Surgical technique

Patients undergoing thoracotomy were positioned on the appropriate lateral side, and a standard posterolateral thoracotomy was performed with division of the latissimus dorsi muscle and sparing of serratus anterior muscle. Division of rib was not performed and the ribs were spread using a Holme-Sellars self-retaining retractor. Patients undergoing VATS procedures had between one and three ports depending on the procedure performed. If more than one port was used, where possible these were placed in the same intercostal space.

A paravertebral catheter was placed under direct vision at the end of the surgical procedure in a number of patients, as outlined in the results

3.2.3 Sample size calculation

Initially we aimed to recruit 125 patients to the study. This allowed a loss of 20% at follow up to give a final sample size of 100. This sample size allowed estimates of acute neuropathic pain within at least 10% of the true population incidence (with 95% confidence intervals). Even if acute neuropathic pain in

thoracic surgery patients was rare, such as the 3% incidence previously described (in all post operative patients), this study sample size would provide a good chance of detecting it (95% power) [174].

If the incidence of acute neuropathic pain was greater than 25% there would be adequate power to detect an important association with chronic neuropathic pain at 3 months (80% power at 5% significance for a risk ratio of 2).

3.2.4 Statistical methods

Pain in patients with a LANSS or S-LANSS score ≥12 was considered to be neuropathic. Relative risks and Odds ratios were used to express and quantify any association between acute neuropathic pain and chronic neuropathic pain, with Fisher's exact test being used to calculate the significance of any such associations in this, and in other, 2x2 contingency tables. Any possible relationships between chronic neuropathic pain and other factors (such as the pre-operative LANSS score) were investigated using stepwise logistic regression analysis with the statistical package STATA. This statistical analysis was performed by the statistician Dr Walter Gregory working on behalf of the Clinical Trials and Research Unit in Leeds. Relative risks and their associated confidence intervals were calculated as described by Altman [256].

3.3 Results

3.3.1 Patient characteristics

115 patients were recruited to the study between October 2007 and September 2008. Fifteen patients were withdrawn from the study. One patient was excluded because of pre-existing neuropathic pain identified by a baseline pre operative LANSS score ≥12. One patient was admitted to intensive care

following surgery and subsequently died. One patient withdrew consent to participate in the study in the post-operative period. Twelve patients were recruited but had their operation cancelled, postponed or did not proceed to VATS or thoracotomy. The number of patients recruited and completing assessments at each stage of the study is presented in figure 3.1.

Analysis of the data was based on the remaining 100 patients. The average age (mean) was 62 (range 17-88). There were 64 males and 36 females in the cohort. Data relating to operation type are presented in table 3.2.

Operation type	N=
Thoracotomy	48
VATS	49
VATS & Mini thoracotomy	2
VATS & thoracotomy	1

Table 3.2 The number of patients receiving VATS and thoracotomy procedures assessed for acute neuropathic pain using the LANSS questionnaire.

VATS = Video Assisted Thoracoscopic Surgery, N = number of patients, LANSS = Leeds

Assessment of Neuropathic Symptoms and Signs.

```
┌─────────────────────────────┐
│   Thoracic surgery patients │
│     recruited to the study  │
│                             │
│          n=115              │
└─────────────────────────────┘
              │
┌─────────────────────────────┐
│   Completed pre-operative   │
│          LANSS              │
│                             │
│          n=115              │
└─────────────────────────────┘
              │
       ┌──────┴──────────┐
┌──────────────┐  ┌──────────────────┐
│  Patients    │  │  Completed post- │
│  withdrawn   │  │  operative LANSS │
│  from study  │  │                  │
│              │  │      n=100       │
│   n=15       │  └──────────────────┘
└──────────────┘           │
                    ┌──────┴──────┐
              ┌──────────┐  ┌──────────┐
              │Completed │  │Completed │
              │ postal   │  │telephone │
              │ S-LANSS  │  │ S-LANSS  │
              │          │  │          │
              │  n=57    │  │  n=30    │
              └──────────┘  └──────────┘
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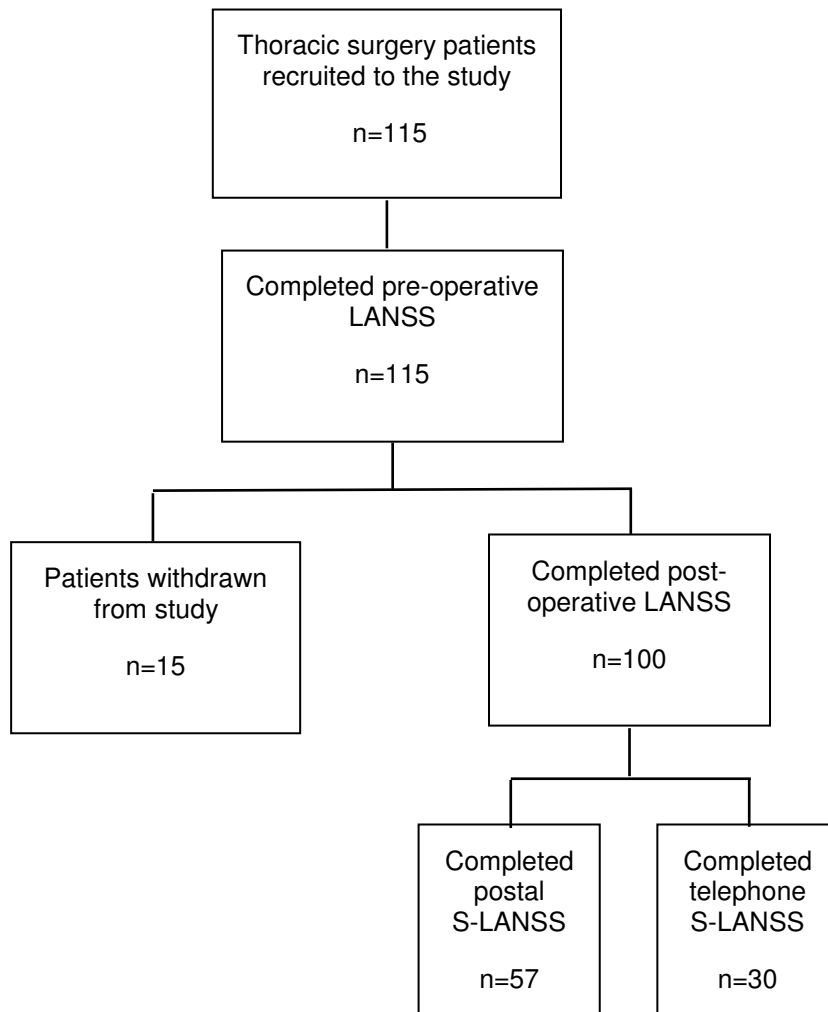
Figure 3.1 The number of patients recruited and completing each stage of the acute neuropathic pain prevalence study.

n = number of patients, LANSS = Leeds Assessment of Neuropathic Symptoms and Signs, S-LANSS = Self report version of the Leeds Assessment of Neuropathic Symptoms and Signs

There was an even split between thoracotomy and VATS procedures, with a small minority having both procedures.

The reason for operation was recorded, with 65 patients having malignant disease. Thirty-one patients had non-small cell lung cancer, 6 had mesothelioma, 20 had metastatic cancers. A variety of other pathologies were recorded including 2 carcinoid, 1 empyema, 1 interstitial pneumonia, 1 leiomyosarcoma, 1 pneumothorax and 1 thymoma.

The different forms of primary post-operative analgesia used are presented according to operation type in table 3.3.

Type of operation	Intravenous morphine(via PCA)	Thoracic paravertebral block	Thoracic epidural	Intercostal nerve block
Video assisted thoracoscopic surgery (VATS)	33 (67%)	24 (49%)	1 (2%)	4 (8%)
Thoracotomy	41 (85%)	39 (81%)	5 (10%	7 (12.5%)
VATS & thoracotomy	3 (100%)	2 (66%)	1 (33%)	0 (0%)
All procedures	77%	65%	7%	11%

Table 3.3 Types of post-operative analgesia used by patients assessed for acute neuropathic pain using the LANSS questionnaire (number of patients and percentage of total)

VATS = Video Assisted Thoracoscopic Surgery, PCA = Patient Controlled Analgesia

3.3.2 Prevalence of acute and chronic neuropathic pain

One hundred patients completed the LANSS score an average (mean) of 3 days post operation (range 1-6 days). Eight patients (8%) developed acute neuropathic pain in the early post-operative period (defined as a LANSS score ≥ 12). None of these 100 patients had pre-operative neuropathic pain identified by pre-operative LANSS screening.

Eighty-seven of the 100 patients completing pre and early postoperative LANSS assessments subsequently completed postal or telephone S-LANSS questionnaires an average (mean) of 110 days following their procedure (range 86-213 days). One patient died during the three months period following their operation and a further 12 patients did not respond to the postal questionnaire or telephone contact.

Of these 87 patients, 19 (22%) had chronic neuropathic pain (defined as an S-LANSS ≥ 12). Eighty five patients completed the numerical rating scale (NRS) component of the S-LANSS questionnaire, revealing 53 (62%) had some degree of chronic pain following their operation. There was a significant difference in the NRS scores when comparing those with chronic neuropathic pain (S-LANSS ≥ 12) with those with chronic nociceptive pain (S-LANSS <12) following their operation, with those with neuropathic pain having more severe pain intensity. The median NRS score for those with nociceptive pain was 1, compared to the median NRS score of 5 for those with neuropathic pain (Mann-Whitney W statistic 2297, $p<0.00001$). The distribution of NRS scores in the neuropathic and nociceptive groups are presented in table 3.4.

NRS score	3-month S-LANSS<12 N (%)	3-month S-LANSS ≥12 N (%)
0	32 (49)	0 (0)
1	9 (14)	0 (0)
2	10 (15)	3 (16)
3	6 (9)	3 (16)
4	1 (1)	2 (11)
5	2 (3)	5 (26)
6	1 (1)	2 (11)
7	2 (3)	2 (11)
8	2 (3)	2 (11)
9	0 (0)	0 (0)
10	0 (0)	0 (0)

Table 3.4 Distribution of numerical rating pain intensity scores (NRS) according to S-LANSS category of neuropathic (score ≥12) or nociceptive (score <12) pain.

S-LANSS = Self report version of the Leeds Assessment of Neuropathic Symptoms and Signs, N = number of patients

Interestingly, there is only a weak correlation between the total early post-operative LANSS score and chronic pain intensity at three-month follow-up (r=0.18, p=0.0466), figure 3.2. Spearman's rank correlation coefficient is non significant (0.12).

Comparing categorical early post-operative LANSS data (dividing patients into nociceptive and neuropathic pain groups) also shows a lack of significant

difference in pain intensity at three-month follow-up (median of 1 and 3.5

respectively, W statistic 3196.5 p=0.09).

Patients with acute neuropathic pain were more likely to have chronic
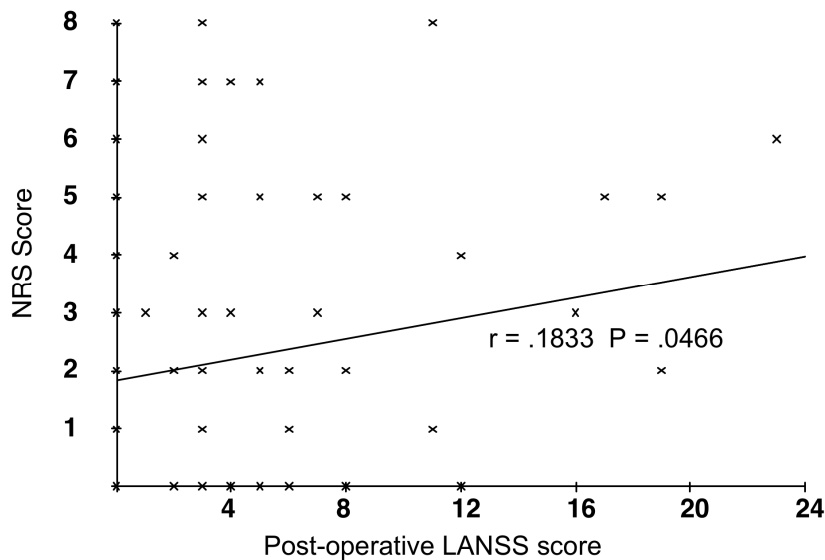
Figure 3.2 Scatter plot showing correlation between early post-operative LANSS score and 3 month pain intensity score.

LANSS = Leeds Assessment of Neuropathic Symptoms and Signs, NRS = Numerical Rating Scale of pain intensity (0-10)

neuropathic pain at 3 months than those without acute neuropathic pain (5/8

(62.5%) vs. 14/79 (18%), relative risk 3.5 (95% C.I. 1.7-7.2). Item one of the

LANSS questionnaire ("Does your pain feel like strange, unpleasant sensations

in your skin? Words like pricking, tingling pins and needles might describe these

sensations") was particularly predictive of 3 month chronic neuropathic pain,

with a relative risk of 4.5 (95% C.I. 2.3-8.7), with 70% of patients who answered

yes to this question developing chronic neuropathic pain compared to 16% of

those who answered "no". Relative risks and odds ratios for the univariate

logistic model prediction of a neuropathic or nociceptive S-LANSS score at 3

months are presented in table 3.5. In a multivariate logistic regression, the other

6 components of the LANSS did not add to the predictive capacity of question

1.

LANSS Item	LANSS Positive post-operatively [n (%)]	S-LANSS Positive at 3 months [n (%)]	Relative Risk (95% C.I.)	Odds ratio (95% C.I.)
Total ≥12	8 (8)	19 (22)	3.5 (1.7 – 7.2)	7.7 (1.5-39.7)
1	11 (11)	25 (29)	4.5 (2.3 – 8.7)	12.6 (2.4-65.6)
2	8 (8)	5 (6)	3.5 (1.7 – 7.2)	7.7 (1.5-39.7)
3	26 (26)	36 (41)	1.8 (0.82 – 3.9)	2.2 (0.74-6.4)
4	20 (20)	22 (25)	2.4 (1.1 – 5.2)	3.4 (1-11.1)
5	17 (17)	8 (9)	2.2 (1.0 – 4.9)	3.0 (0.89-10.3)
6	4 (4)	27 (31)	1.2 (0.2 – 6.6)	1.2 (0.12-12.5)
7	55 (55)	41 (47)	1.8 (0.77 – 4.4)	2.2 (0.72-6.5)

Table 3.5 Numbers (%) of thoracic surgery patients that were LANSS positive post-operatively; numbers that were S-LANSS positive at 3 month follow-up; relative risk and odds ratios for positive scores at 3 months if positive post-operatively

n = number of patients, C.I. = confidence interval, LANSS = Leeds Assessment of Neuropathic Symptoms and Signs, S-LANSS = Self report version of the Leeds Assessment of Neuropathic Symptoms and Signs

Unlike the pain intensity (NRS) measure at 3 months, there was a significant

correlation between the total early post-operative LANSS score and the 3-

month S-LANSS score (r=0.33, p<0.001) (figure 3.3).

Three patients who demonstrated acute neuropathic pain characteristics did not

go on to develop chronic neuropathic pain. One patient with acute neuropathic

pain characteristics had a NRS score and S-LANSS score of 0 at the three-

month follow-up. Of the other two patients with acute neuropathic pain who did

not develop chronic neuropathic pain, both answered "yes" to either item 3 or

item 6 of the three month S-LANSS, suggesting that they may have had

symptoms or signs of allodynia, yet their total S-LANSS scores were 3 and 5.

This is much lower than the 12 needed to make a diagnosis of chronic
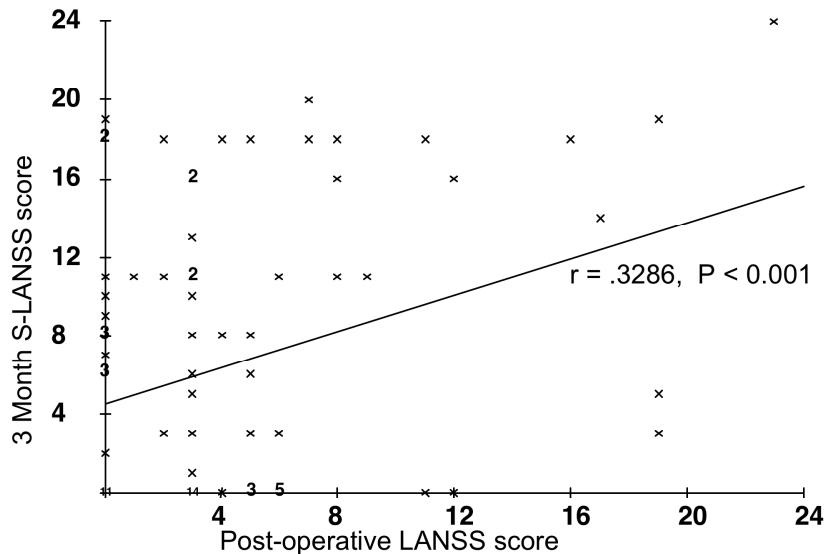
neuropathic pain.

Figure 3.3 Scatter plot showing correlation between total post-operative LANSS score and 3 month S-LANSS score.

LANSS = Leeds Assessment of Neuropathic Symptoms and Signs, S-LANSS = Self report version of the Leeds Assessment of Neuropathic Symptoms and Signs.

There was no correlation between chronic neuropathic pain and gender, type of

operation or whether the underlying disease diagnosis was malignant or benign.

Older patients were more likely to have chronic neuropathic pain (p= 0.04);

although this was not significant once the post-operative LANSS score was

included in a multivariate predictive model. Univariate and multivariate logistic

regression analysis demonstrated no single analgesic technique was

associated with the subsequent development of chronic neuropathic pain.

Interestingly, using cut off points other than 12 on the LANSS to define pain as nociceptive or neuropathic in origin reduced the correlation between post-operative LANSS and 3 month S-LANSS score, perhaps confirming this cut off point in the early post-operative period as appropriate.

3.4 Conclusions

The results of this study demonstrate that 8% of patients undergoing major thoracic surgery develop acute neuropathic pain characteristics in the immediate post-operative period and that 22% of patients have symptoms of predominantly neuropathic pain three months after their operation. Furthermore, the study demonstrates the presence of acute neuropathic pain symptoms and signs are significantly associated with the development of chronic neuropathic pain, suggesting that for some patients who develop neuropathic pain following surgery, the process can be identified early in the post-operative period using verbal descriptors and simple bedside examination techniques.

3.4.1 Acute neuropathic pain

Prior to this research, the prevalence of acute neuropathic pain following thoracic surgery was not known. Although Hayes (2002) estimated the incidence of acute neuropathic pain as 1-3% of all surgical patients, this study only included one case following thoracotomy, and patients were not screened for pre-existing neuropathic pain.[174] In addition, the authors only investigated patients referred to the acute pain service.[174] However, similar results were reported in a more recent study: Sadler et al., (2012) used the LANSS and DN4 screening tools to estimate acute neuropathic pain prevalence in a population of 165 patients undergoing orthopaedic or general surgery, one day after their

operation.[257] The LANSS identified 5 (3%) patients with neuropathic pain, compared to 7 (4%) identified with the DN4 questionnaire.[257]

Although both these results differ from the prevalence of acute neuropathic pain of 8% in the cohort of patients presented in this thesis, this may in part be explained by the difference in surgery type. As discussed previously, thoracic surgery is particularly associated with nerve damage, and the prevalence of chronic neuropathic pain is significantly higher in this group compared to orthopaedic or general surgical patients, so logically, the incidence of acute neuropathic pain would be expected to be greater amongst thoracic surgery patients.

In a recent study investigating patients having surgery for iliac crest bone harvest, chronic neuropathic pain (at 3 months) was present in 23% of patients investigated, a proportion almost identical to that found in our study following thoracic surgery.[258] This study also collected DN4 data in the early postoperative period at 48 hours, and despite using a different screening tool described 8 (10%) patients with positive DN4 scores at this stage developing chronic neuropathic pain. Unfortunately, the exact prevalence of acute neuropathic pain was not reported. However the incidence was at least 10% or higher, similar to the 8% reported by our study, supporting the hypothesis that acute neuropathic pain is more common in surgery where nerve damage and thus chronic neuropathic pain is more likely.

3.4.2 Chronic neuropathic pain

This study found that 22% of patients have predominantly neuropathic pain 3 months after thoracic surgery. At the time the study started recruiting in 2007,

little data was available describing the prevalence of chronic neuropathic pain in the post thoracic surgery population.

Gotoda et al., (2001) reported that 28% of post-thoracotomy patients had pain with paraesthesia/dysaesthesia, and 11% had allodynia 1year after surgery and concluded that "nerve impairment rather than simple nociceptive impact may be involved in this syndrome".[137]

Maguire et al., (2006) performed a retrospective survey of 600 thoracic surgery patients, enquiring about the presence of 5 symptoms suggestive of neuropathic pain.[253] Their results suggested that neuropathic pain may be a component of the pain experience in a proportion of post thoracic surgery patients: of the 45% of patients with chronic pain after their surgery, between 35% and 83% answered 'yes' to each of the five verbal descriptors of neuropathic pain.[253] However, whilst the results of this study point to neuropathic pain playing a role in the chronic pain experience of thoracic surgery patients, it did not allow an estimation of the prevalence of this problem, and was limited by a number of methodological issues.

Firstly, the study was retrospective, and failed to exclude pre-existing neuropathic pain. Secondly, the time period between surgery and questionnaire completion ranged from 7 months to 7 years, making a point estimate of prevalence impossible. Lastly, the study did not use a validated method of diagnosing neuropathic pain, instead it used the first 5 questions of the S-LANSS questionnaire (without the 2 self examination items). The validity of these questions relies on their use as a weighted overall score, and a positive

response to one or more of the questions does not necessarily result in a diagnosis of neuropathic pain.

Similarly, other studies have demonstrated the presence of neuropathic descriptors in the post thoracic surgery population, however these are interventional rather than epidemiological studies and methodological issues prevent accurate estimation of neuropathic pain prevalence.[259-261]

Steegers et al., (2008) used a validated questionnaire (PainDETECT) to determine the incidence of chronic neuropathic pain following surgery.[255] They found that of the 40-47% of patients with chronic pain following their surgery, 53% had at least probable neuropathic pain. Despite the retrospective nature of this study, again performed at varying time-points following surgery (6-38 months), and the use of a different screening tool, the calculated incidence of neuropathic pain of 21-25% is remarkably similar to that found in our study (22%).

In a more recent study, Guastella et al., (2011) prospectively investigated 54 patients undergoing thoracic surgery, assessing them for neuropathic pain 6 months after their operation.[262] Using a combination of verbal descriptors and sensory examination (including tests for mechanical and thermal allodynia and sensory deficits to touch and pin-prick) allowed the authors to estimate the prevalence of probable neuropathic pain according to the recent diagnostic grading system proposed by a consensus panel of international experts.[138] Their results show an incidence of neuropathic pain of at least 29% six months following thoracotomy. Interestingly, the DN4 screening questionnaire was also completed at the time of assessment, and all patients exhibiting positive results

with this screening tool also fulfilled the criteria for probable neuropathic pain according to the grading system, bar one person in whom sensory loss was not demonstrated. Overall, the grading system identified 21 patients with probable neuropathic pain, and the DN4 17 patients. Both this, and the similarity of results with the study presented in this thesis suggest using screening tools is a valid way of estimating neuropathic pain prevalence in this population, although in keeping with original validation studies they are likely to underestimate the true incidence of neuropathic pain.[263] This observation is supported by data collected in a systematic review of the neuropathic component of persistent post-surgical pain, which showed that by grading neuropathic pain as probable or definite (using the consensus grading system) the prevalence of neuropathic pain following all types of thoracic surgery (including sternotomy) was 66% of those with persistent pain, compared to 52% in studies using questionnaire screening tools.[135]

3.4.3 Can postoperative pain descriptors predict chronic neuropathic pain?

The results presented in this chapter demonstrate that the presence of neuropathic pain descriptors in the immediate post-operative period predict the development of chronic neuropathic pain. A LANSS diagnosis of acute neuropathic pain results in a relative risk of developing chronic neuropathic pain of 3.5 (OR 7.7). Interestingly, answering question 1 positively was particularly predictive of developing chronic neuropathic pain, with a relative risk of 4.4 (OR 12.6). This question, related to the sensation of unpleasant dysaethesias, carries a high LANSS weighting in the total score meaning it was particularly

associated with a diagnosis of neuropathic pain in the original LANSS validation study.

Whilst other studies have demonstrated that pain intensity following thoracic surgery is associated with the development of chronic pain, the predictive nature of neuropathic pain descriptors for the development of chronic neuropathic pain has not previously been described.[167] Hayes et al., (2002) noted a strong association between the diagnosis of acute neuropathic pain and the presence of persistent pain 6-12 months later, although were not able to say if this pain was neuropathic in nature.[174] In their study, 78% of those with acute neuropathic pain went on to develop chronic post-operative pain.[174]

Interestingly, two subsequent studies tend to support the predictive nature of neuropathic pain descriptors. Bouhassira et al., (2012) using the DN4 screening questionnaire demonstrated that a DN4 diagnosis of neuropathic pain made during the first 7 days of herpes zoster infection was an independent predictor for the development of post herpetic neuralgia at 3 months (OR 1.78 95% C.I. 1.03-3.06).[264] The authors conclude that pain quality, rather than just pain intensity confers greater risk of persistent herpes zoster related pain.[264]

In a study of the predictive factors for the development of chronic neuropathic pain 3 months after surgery for Iliac crest bone harvest, Martinez et al., (2012) found that the DN4 screening tool when performed 48 hours after surgery independently predicted the development of chronic neuropathic pain (OR 1.94).[258] The authors conclude that a major finding of their study was the predictive nature of neuropathic pain characteristics in the early postoperative period.[258] Interestingly, the odds ratios for the predictive qualities of the LANSS

in our study were much higher than those presented using the DN4 (7.7 vs 1.94).

3.4.4 Limitations of the research

It is important to realize that not all patients with acute neuropathic pain characteristics go on to develop chronic neuropathic pain. In the cohort studied, three patients with acute neuropathic characteristics did not develop chronic neuropathic pain. There are a number of potential reasons for this.

Firstly, the natural history of acute neuropathic symptoms and signs may be that over a third of cases spontaneously resolve in the first three months. For example, a painful neuropraxia caused during surgery slowly resolves with time. This hypothesis is supported by evidence from longitudinal studies of chronic post thoracotomy pain patients, which demonstrate the incidence of pain falling with time.[146, 250, 252]

Secondly, because of the small number of patients with acute neuropathic pain characteristics, confounding factors such as differing medications may have influenced the results. For example, it is not clear what effects anti-neuropathic pain medications used during the perioperative period have on the development of chronic neuropathic pain. In a study of patients undergoing amputation, the anti-neuropathic pain medication gabapentin started pre-operatively and continued for 30 days post-operatively failed to prevent the development of phantom limb pain.[265] In contrast a small study showed a promising reduction in chronic pain following breast cancer surgery when perioperative gabapentin was combined with local anaesthetics, although this study has been criticized for methodological flaws.[266, 267] Pregabalin has also shown promise in reducing

the incidence of chronic neuropathic pain following surgery when given as a preventative medication in the peri-operative period. In a study of patients having total knee arthroplasty, pregabalin given pre-operatively and for 14 days post-operatively appeared to have a significant preventative effect on the development of chronic neuropathic pain following surgery, with no patients in the treatment group developing chronic neuropathic pain (compared to 8.7% in the placebo group).[268] The effects of peri-operative gabapentin and pregabalin were recently summarized in a meta-analysis that described preventative effects of both drugs on the development of chronic post-surgical pain (pooled OR 0.52 and 0.09 respectively).[269]

Other drugs may have similar properties. In animal models of neuropathic pain the antibiotic minocycline, when commenced in advance of traumatic nerve injury attenuated the development of chronic neuropathic pain.[270] Similar effect have been noted with amitriptyline.[271] This raises the possibility that perioperative medications may influence the development of chronic neuropathic pain.

This study did not specifically screen patients pre-operatively for the presence of anti-neuropathic pain medications. However, review of the acute pain notes for the three patients who had acute neuropathic pain characteristics but did not develop chronic neuropathic pain revealed that one patient was started on gabapentin in the postoperative period (4 days following their operation). This patient had a 3-month NRS and S-LANSS score of 0. The peri-operative administration of these drugs may therefore have been a confounding factor in the results of both acute and chronic neuropathic pain prevalence.

A further important observation is that the majority of patients who developed CNP (74%) did not have neuropathic pain characteristics in the immediate post-operative period, although they had significantly higher average LANSS scores compared to patients who did not develop CNP. It is not clear whether this reflects a different pathophysiological process, delayed onset of nerve damage, or if it reflects a reduction in the sensitivity of the LANSS score when used in the early post-operative period. Interestingly Martinez et al., (2012) reported similar results, noting that in 57.5% of patients with chronic neuropathic pain at 3 months after surgery, neuropathic pain developed between 48 hours and 3 months after their operation.[258]

The S-LANSS contains a numerical rating scale of pain intensity, however in contrast, the LANSS screening tool does not. Pain intensity data was therefore not collected during the immediate postoperative period. In addition, although basic details of analgesic use was recorded, data on the quantities of analgesics used was not. Consequently, it is impossible to exclude opioid induced hyperalgesia as a potential confounding factor contributing to neuropathic pain symptoms in the immediate postoperative period.

Although the LANSS score has been validated in a mixed population of patients with neuropathic pain, it has not been specifically designed for use in the early post-operative period and the behaviour of the scale may be affected by the intensity of the nociceptive pain experienced following an operation.

No work has been published validating a screening tool such as the LANSS scale in the post-operative period. The LANSS has however been used in other acute pain contexts, such as investigating the neuropathic pain component of

acute whiplash injury.[272] In addition, further analysis of the results of this study showed using cut-off points other than 12 to define nociceptive or neuropathic pain (such as 11 or 13) reduced the correlation between the post-operative LANSS and three month S-LANSS, suggesting that 12 is an appropriate cut-off point assuming that post-operative neuropathic pain predicts the development of chronic neuropathic pain.

Following the publication of a recommended grading system for neuropathic pain in 2008, it could be argued that diagnosing neuropathic pain in the acute post-operative setting should be done based on the presence of pain in a neuroanatomically plausible distribution, and the use of confirmatory diagnostic tests (demonstrating negative or positive sensory signs, and a lesion or disease explaining neuropathic pain) to give a diagnosis of definite neuropathic pain (figure 3.4).[138]
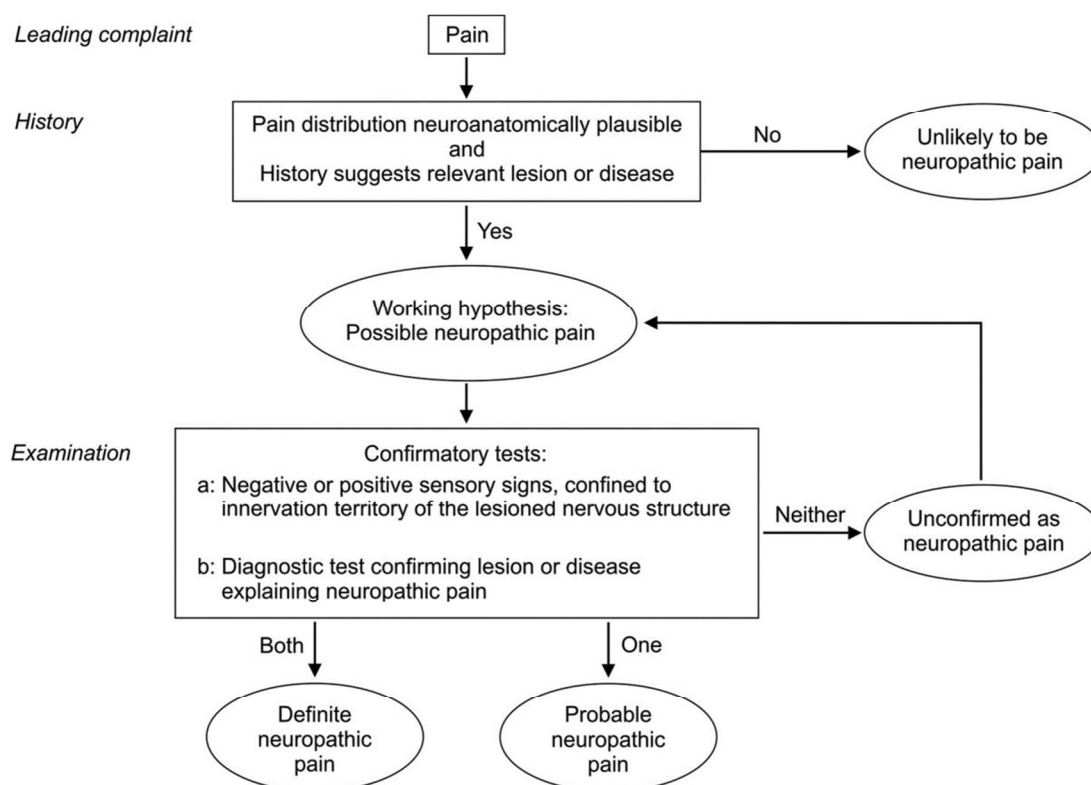
Figure 3.4 Flow chart explaining the consensus grading system for the diagnosis of neuropathic pain (from Treede et al., 2008).

Pain is categorized as unlikely, possible, probable or definitely neuropathic according to a hierarchy of signs and tests.

However, there are a number of difficulties with using this approach in the immediate post-operative period. Firstly, patients may have pain in a neuroanatomically plausible distribution, although the majority of this is likely to be nociceptive from the tissue damage of the operation rather than neuropathic. Secondly, the usefulness of sensory testing in the post-surgical pain setting has been questioned. In the chronic post-surgical pain setting, quantitative sensory testing is unable to differentiate between patients with and without pain after hernia repair, mastectomy or mandibular split osteotomy.[273-275] The implication is that neuropathic pain may not develop, even after significant sensory abnormalities. Similar results have been demonstrated in patients following

thoracic surgery. Quantitative sensory testing of thermal and mechanical stimuli 2 years after VATS surgery showed no significant differences between those patients with pain, and pain-free patients.[276] Similarly, nerve injury judged by QST is common in both pain and pain free patients following thoracotomy.[67] If quantitative sensory testing is unable to differentiate patients in the chronic pain setting, it is less likely to do so in the acute post-operative period when there is also a significant nociceptive component present. Sensory testing alone appears to be less predictive of the development of chronic neuropathic pain than screening tools. Martinez et al., (2012) performed mechanical sensory testing 48 hours after surgery for Iliac crest bone harvest and found only one variable, area of hyperalgesia, to be weakly predictive of the development of chronic neuropathic pain with an odds ratio of 1.02.[258] This compared to a higher odds ratio of 1.9 when they used a diagnostic screening tool.

A further objective test of nerve function – nerve conduction studies, when performed at the time of operation, failed to predict those who would go on to develop chronic pain after thoracic surgery.[66]

Diagnosing acute neuropathic pain is therefore challenging. Conventional approaches to assessing nerve damage do not seem to correlate with the development of chronic neuropathic pain as might be expected, and the most predictive tools appear to be screening questionnaires that to a greater or lesser extent rely on verbal descriptors of pain quality.

Despite this, more work is needed to develop a validated tool to aid the diagnosis of neuropathic pain in the immediate postoperative period. Both the face validity and construct validity of using tools such as the LANSS is

questionable. The LANSS was validated in a mixed population of chronic pain patients, and did not include patients in the immediate post-operative period. In addition, some of the items of the LANSS tool appear to lack face validity when used in this context. For example, question 2, asks whether the skin in the area of pain looks different from normal. This would be an expected finding following surgery where an inflammatory healing process is occurring.

Because of concerns about the validity of using screening tools such as the LANSS in the immediate post-operative period, and the difficulties of using other confirmatory tests for neuropathic pain in this context, further investigation of methods for diagnosing acute neuropathic pain are warranted. In the face of uncertainty about the best way to diagnose acute neuropathic pain, it was hypothesized that acute pain specialists are likely to be diagnosing neuropathic pain in clinical practice, and therefore investigating what criteria are being currently used would be useful. The results of a Delphi survey investigating this are presented in Chapter 4.

4 Diagnosing postoperative neuropathic pain: a Delphi survey of experts

4.1 Introduction

The previous chapters of this thesis have explained the challenging nature of diagnosing neuropathic pain, a clinical condition that has a definition, but no universally accepted diagnostic criteria. Such challenges are compounded in the acute postoperative period by a concurrent nociceptive pain component, perioperative interventions that may alter sensory thresholds and symptoms and signs associated with tissue healing after surgical trauma. Consequently, the face validity of using existing tools to aid the diagnosis of neuropathic pain in this context may be questioned.

It was hypothesized that despite a paucity of research data, acute pain specialists are likely to be diagnosing acute neuropathic pain regularly in the clinical setting. They are likely to be using judgment (based on knowledge and experience) rather than research data alone to achieve this. The specific aim of the research presented in this chapter was to obtain an expert agreed list of pain characteristics or investigations that are considered important in the diagnosis of a significant neuropathic pain component to acute postoperative pain. This was performed using the Delphi consensus technique, a method of eliciting and aggregating knowledge and judgments in a transparent and structured way.

4.2 Consensus methods in qualitative research

Consensus methods are a means of approaching a problem where conflicting or absent scientific evidence exists.[277] They are, in essence a way of collaborative problem solving, with the aim of determining the extent to which a group of individuals agree about a given issue or topic. This type of methodology can allow a broader spectrum of information to be considered than is commonly used in more quantitative approaches (such as meta-analysis), and can be particularly useful where published information is inadequate. Broadly, there are three common approaches to building consensus: the nominal group technique, the consensus development conference and the Delphi process.[277]

4.2.1 Consensus conference

Consensus conferences tend to be organized when agreement on an important topic is needed. The process has been used extensively by the US National Institutes of Health and also by other countries including the UK and Canada to reach consensus on topics such as the treatment of stroke and renal failure.[278, 279] A select group of experts are chosen to hear evidence presented by various interest groups or other experts on the topic, and are allowed to ask questions. This group then retires to deliberate amongst themselves, in a manner similar to that of a jury in a trial, with a chairperson responsible for controlling the discussion. Although consensus is encouraged, members may hold minority or alternative views, and a vote may be used to reach judgment on a decision.[279, 280] Although face to face discussions of this nature can aid group understanding of a topic, organizing conferences can be logistically challenging, expensive and prone to bias by strong willed individuals within the chosen expert group.[280]

In order to overcome some of the disadvantages of the consensus conference process, other consensus development methods, such as the nominal group technique, use a much more structured format of group discussion.

4.2.2 Nominal group technique

The nominal group technique uses a meeting involving a group of experts to rate, discuss, and then re-rate a series of questions about a specific issue. A facilitator who asks experts to take turns in contributing their views on the topic in question leads the meeting. There may be group discussion surrounding the issues identified, and the experts then rank each idea. The rankings are presented to the group, followed by further discussion and re-ranking in order to try and gain a consensus of opinions.[280]

This method has been used widely to solve problems in areas ranging from education and industry to social services and healthcare, and has a number of features that make it an attractive method for generating ideas and consensus opinions.[281] Ideas can be generated in a short space of time, and consensus achieved in a single meeting. The method encourages equal participation from panelists and the process of reaching consensus is transparent to all those participating.[280] In particular, nominal group techniques seek to prevent too much focus on a particular idea, at the expense of exploring the problem thoroughly.[282] Each person in the panel is more likely to work on the problem in hand, rather than leaving the generation of ideas to other panelists.[282] As the facilitator controls the discussion closely, and each participant has the opportunity to express their views in turn, the risk of the discussion being dominated by a few vocal members is reduced. Unfortunately, although the nominal group technique has been modified to allow the first round to be

performed by postal questionnaire, ultimately a face to face meeting of expert

panelists is required, which can lead to logistical difficulties where experts may

be geographically spread across regions or even globally.

4.2.3 Delphi consensus method

The Delphi consensus method offers a potential solution to the logistical

problems of holding a face-to-face meeting of experts in a particular field.

Developed in the 1950's by the RAND corporation in America, the Delphi

process was originally used by the US government to try and predict the impact

of technology on inter-continental warfare at the time of the cold war.[280] This

was an area where at the time, lack of scientific information made traditional

forecasting methods unreliable. Based on the assumption that individual

statistical predications would be more accurate than the conclusions of

unstructured group opinions, a consensus method was developed that required

experts to give their opinion on the probability, intensity and frequency of enemy

attacks and the number of atomic weapons needed to destroy specific

targets.[280] The aggregated views of the group were fed back to participants,

and the process repeated until consensus emerged. The term 'Delphi' was

coined by Abraham Kaplan, a philosopher working at the time for the RAND

corporation, after the Greek oracle said to have the power to predict the

future.[277]

The Delphi process is similar to that of the nominal group technique, the main

difference being the use of surveys rather than conference meetings to gather

expert opinion (with subsequent anonymity of expert views). The 'classical'

Delphi involves a preliminary survey round where participants are asked broad,

open-ended questions on a specific topic. This is used to generate ideas and

opinions, which may not be elicited by other means of information gathering (such as literature reviews), and in the healthcare setting can reflect clinical experience as well as knowledge of scientific research on the topic. These ideas and opinions are grouped together into common themes that are typically formed into a series of statements in the form of a questionnaire. The questionnaire is sent out to the panel of experts as round 2 of the Delphi process. The experts are asked to rate the degree to which they agree or disagree with the statements in the questionnaire. The questionnaires from round 2 are analyzed and the average level of agreement for the group as a whole is calculated for each statement or question. This is then used as feedback to individual experts in round 3. In round 3, the same questionnaire is sent back to panelists, this time with the addition of the overall group score for each statement or question and a reminder of the individual experts previous score. The experts have the opportunity to change their individual scores in light of the group result. The re-rated questionnaires are then analyzed for the degree of consensus achieved. In theory the process can be repeated until a predetermined level of consensus is achieved or diminishing changes mean opinions and scores are likely to remain the same.

A number of different forms of Delphi surveys have evolved since the early development of the classic Delphi approach. These include the 'modified Delphi', whereby the first round is often replaced by face-to-face meetings or focus groups and the 'Policy Delphi', which uses expert agreement to define future policy on a given topic.[283, 284] Further modifications of the classical Delphi have capitalized on the technological revolution of the latter part of the 20[th] century, resulting in the e-Delphi (administered by email or online rather than by

post), the online Delphi (questionnaires completed and submitted online) and the technological Delphi (similar to the consensus conference, but making use of electronic devices to allow voting and instant feedback of group scores on a topic).[280] The proliferation of modified techniques has led to concerns that the credibility of the original Delphi process is being threatened.[280]

A further threat comes from the (somewhat ironic) lack of consensus over Delphi methodology, and absence of universal guidelines. With few established rules to guide the design of Delphi studies, a confusing variety of formats and variations exist.[285] Beyond the generally accepted criteria that the Delphi process should give feedback to participants, and have at least two rounds, most other aspects of methodology including the size and composition of the expert panel and definition of consensus, are subject to variation in the literature, both in health related research and also outside of medicine.[279, 286, 287]

Perhaps the most important consideration in the Delphi process is the choice and identification of the expert panel. The use of credible 'experts' in the appropriate field is cited by many as an important factor in consensus development methods.[277, 281, 282] However, the definition of 'expert' may vary depending on the issue being studied, and may include an experienced clinician, research scientist or patient with experience of a disease.[288] As such, an expert can be defined as a group of informed individuals, who are specialists or who have knowledge about a specific subject. [283, 289, 290]

The exact composition of a panel of experts may vary considerably, although broadly can be defined as homogenous or heterogeneous with regards to factors such as demographics, education, job, experience, geographical

location etc. Heterogeneity probably leads to better performance and enhances the credibility of the consensus process, although some evidence suggests heterogeneity may cause conflict and difficulty reaching a common conclusion.[282, 288]

The size of the expert panel can vary dramatically from single figures to thousands of individuals.[280, 291] Although large panel sizes have been advocated by some as a means of ensuring reliable results, there is little empirical evidence to support such a proposition.[282, 288, 292] Large panel sizes can be difficult to co-ordinate, and participation may become more unequal.[293] In addition, they may be prone to higher rates of attrition between Delphi rounds.[294] Theoretical studies investigating the optimum panel size suggest there is little improvement in group validity by increasing panel sizes beyond 10 individuals.[295, 296] Supporting this theoretical view of consensus methodology is a study by Richardson (1972) that demonstrated improvement in the reliability of ratings with up to 10 group participants, beyond which it began to level off.[297] In studies of group decision making, the effect of size is slight and few effects have been found in studies comparing 6 and 12 person groups.[298-301] The conclusion of the Health Technology Assessment review of consensus methodology in 1998 was that with a group size less than 6, reliability declines rapidly, and with a group size over 12, improvements in reliability are subject to diminishing returns.[282] A recent systematic review of healthcare Delphi studies reported an average panel size of 17 (range 3-418).[302]

A further area of Delphi methodology that varies from study to study is the definition of consensus. However, before considering the definition of consensus, it is necessary to summarize the results of each round. This

typically takes the form of aggregating individual judgments in some way. One of the most common methods of achieving this is by calculating the median and interquartile range of the panelist scores. This has the advantage of being independent of extreme values and less sensitive to skew in the distribution of responses, as long as the panel is greater than 8 and the distribution is not markedly bimodal.[279] Once the frequency and distribution of responses for each item or question have been calculated, the next step is to determine which, if any, have achieved consensus.

For most, consensus represents collective agreement, or put more formally "a condition of homogeneity or consistency of opinion among the panelists".[280, 303] The point at which consensus is reached however, and the statistics applied to this aspect of Delphi studies varies considerably. In their systematic review of Delphi studies, Boulkedid et al., (2011) reported 5 main methods of achieving consensus.[302] Thirty five percent of studies used median scores above a predefined threshold combined with a high level of agreement among panel members. In 16% of studies, only a median score above a certain predefined level was used. In 15% of studies, the proportion of experts who rated the item highly had to be greater than a predefined threshold (e.g. 75% of experts rating the item greater than 7/10). Thirteen percent of studies used RAND UCLA criteria, and 3% used interpercentile range and interpercentile range adjusted symmetry. Other statistics used to gauge agreement, include the kappa statistic, intra-class correlation coefficients and Cronbach's alpha.[279, 303] There remains however no agreed standard method for determining group consensus, and arbitrary consensus standards are common.[280]

4.3 Methods

A three round, internet based Delphi survey of acute pain experts was designed. After review by the Leeds ethics committee, the project was not judged to need formal ethics committee review by an NHS research ethics committee.

4.3.1 Choice of experts

Experts with clinical or research experience of diagnosing and treating acute neuropathic pain in the immediate postoperative period were sought to participate in the Delphi expert panel from two main sources. Firstly, from the membership of the British Pain Society's Acute Pain Special Interest Group, whose aim is to provide a forum for members of the British Pain Society with a special interest in acute pain. Secondly, by a literature search of national and international authors who had previously published research on the subject of acute neuropathic pain. Potential participants identified by these two means were emailed an invitation to participate in the Delphi survey. The email contained a web-link to an online information page explaining the objectives of the survey and Delphi process (appendix 3). From this page, participants could access round 1 of the Delphi survey via a web-link.

All rounds of the Delphi were conducted via a secure internet email survey system (http://www.defgo.net).

4.3.2 Round 1

Those acute pain experts who read the information web page and decided to participate in the Delphi survey were taken via a web-link to the first round Delphi questionnaire. In keeping with classical Delphi methodology, the round 1

questionnaire was designed to generate ideas around the topic of acute
neuropathic pain. Specifically, participants were asked open questions to
develop an initial list of symptoms, signs and investigations considered useful or
important in diagnosing acute neuropathic pain. Additionally, barriers to the
diagnosis of acute neuropathic pain were explored, as were the degree to which
anti-neuropathic pain medications were used in the postoperative setting. The
questions included in the round 1 survey are presented in appendix 4.
Participants completing round 1 were asked to leave contact email details if
they wished to become a panelist in further Delphic rounds.

The symptoms, signs and investigations identified in round 1 were collated and
grouped together under common headings. From this information, plus that
obtained from a literature search on the topic, a new questionnaire was
designed and distributed as round 2 of the Delphi process to panel members
from round 1 who agreed to continue to participate by leaving their email
contact details.

4.3.3 Round 2

A copy of the round 2 questionnaire is included as appendix 5. The
questionnaire asked panelists to rate the importance of each acute neuropathic
pain diagnostic parameter on a numerical likert scale (anchored 1 "not
important" to 10 "very important"). Rather than asking participants to rank the
items in order of importance, the importance of each item was judged
independently of the others (so all items could potentially be rated as very
important). As in round 1, each panelist completed the questionnaire online, via
a web-link sent in an email.

The results of round 2 were aggregated and summarized as the median of the attributed weights and inter-quartile range (IQR) for each item. All statistical calculations were performed using IBM SPSS Statistics Version 20 (SPSS Inc., Chicago, IL, USA). These values were fed back to individual panelists during round 3.

4.3.4 Round 3

In round 3, the same questionnaire as round 2 was used with the addition of the group median and IQR results clearly stated for each item. In addition, each participant was reminded of his or her initial score for the item (from round 2). Each panelist was given the opportunity to change their round 2 score in light of the group median and IQR result, on the same 1 to 10 numerical rating scale.

Following round 3, revised median and IQR results were calculated. Questionnaire items were considered important if the median score was ≥ 7. Expert agreement or consensus was defined as an IQR ≤ 3. Cronbach's alpha was used to investigate internal consistency among panellists and also for parameters considered important and achieving agreement. Internal consistency was also calculated for non-important items.

4.4 Results

4.4.1 Round 1

Thirty-four specialists who received the invitation email opened the round 1 survey via a web-link in the online information page. Twenty-four participants answered 1 or more of the survey questions, with 14 leaving contact details, indicating they would like to participate further in the Delphi process. Of the 14 leaving contact details 13 were based in the UK, with 1 person from Australia.

Five specialists had > 10 years experience as consultants, 1 had 5-10 years

experience and 2 reported 1-5 years experience (6 left the question

unanswered).

The symptoms, signs and investigations identified by participants in the round 1

survey, in conjunction with those identified by literature search, were collated

and grouped under common categories. Round 1 of the Delphi process

generated a number of items that may be useful in identifying acute neuropathic

pain, and are presented in table 4.1.

Fifty percent (n=7) of respondents used current screening tools in the diagnosis

of acute neuropathic pain. Examples given included the LANSS, PainDetect

and locally developed questionnaires.

Table 4.1 Items that may be useful in the diagnosis of acute neuropathic pain identified from round 1 of the Delphi process

QST = Quantitative Sensory Testing, MRI = Magnetic Resonance Imaging, NSAIDs = non steroidal anti-inflammatory drugs

Temporal nature	Descriptive nature	Signs	Surgical details	Therapeutic Response	Investigations
Spontaneous	Sharp	Skin colour	Type of surgery	Difficult to manage pain	Screening tools
Paroxysmal	Shooting	Sweating	Site of surgery	Poor response to opioids/NSAIDS	QST
Extends beyond expected	Stabbing	Dermatomal distribution		Response to antineuropathic agents	MRI
duration	Lancinating	Allodynia			
	Burning	Hyperalgesia			
	Unexpected intensity	Altered skin sensation			
	Pins and needles	Signs of autonomic			
	Dysaesthesias	dysfunction			
	Pain in area of numbness				

A number of obstacles to identifying acute neuropathic pain were identified, including distinguishing it from nociceptive post-operative pain, lack of awareness of the problem, cross cultural communication difficulties and lack of agreed diagnostic criteria.

Sixty seven percent (n=8) used anti-neuropathic pain medications in the immediate post-operative period, with 55% (n=6) using them on a weekly basis. 60% (n=6) used anticonvulsants, 40% (n=4) used antidepressants, 30% (n=3) used NMDA receptor antagonists.

4.4.2 Round 2

Using the symptoms, signs and investigations identified in round 1, a round 2 questionnaire was developed and sent to the 14 participants who agreed to continue with the Delphi process. The participants were asked to rate the importance of each symptom, sign or investigation on a numerical rating scale. 10 panelists completed the round 2 questionnaire and the results are presented in table 4.2.

4.4.3 Round 3

The 10 panelists completing round 2 of the Delphi process were emailed a link to the round 3 questionnaire, and asked to consider changing their rating for each pain characteristic in light of the group median and IQR results. Two panelists changed their results in light of the group results and the recalculated aggregate results are presented in table 4.2. Items achieving consensus following the 3 Delphi rounds are presented in table 4.3.

ANP Identifier	Round 2					Round 3	
	Valid (n=)	Missing (n=)	Median	IQR	Range	Median	IQR
Pins & needles	9	1	9	3.5	4-10	9	3.5
Dysaesthesias	9	1	9	2.5	7-10	9	2.5
Good response to antineuropathics	10	0	9	1.5	7-10	9	1.25
Burning	10	0	8.5	3	6-10	8.5	3
Allodynia	10	0	8.5	2.25	7-10	8	2.25
Hyperalgesia	10	0	8.5	2.25	6-10	8.5	2.25
Shooting	10	0	8	2.25	7-10	8	2.25
Unpleasant sensations	9	1	8	3.5	6-10	8	3.5
Difficult to manage	10	0	8	3	4-10	7.5	1.5
Screening tools	10	0	8	4.25	5-10	8	5
Lancinating	10	0	7.5	4	3-10	7.5	4
Hyperpathia	10	0	7.5	4.25	5-10	7.5	4.25
Autonomic features	10	0	7.5	4.25	3-10	7.5	4.25
Poor response to opioids	10	0	7.5	1	6-9	8	1.25
Spontaneous	9	1	7	2.5	4-10	7	2.5
Stabbing	10	0	7	5.5	2-10	7	5.5
Colour	10	0	7	5.75	1-10	7	5.75
Response to IV lignocaine	10	0	7	3.5	5-10	7	3.5
Paroxysmal	8	2	6	2.75	2-9	6	2.5
Sharp	10	0	5	5.5	1-10	4.5	5.5
QST	9	1	5	3.5	1-10	5	4.5
Radiology	9	1	5	2.5	0-7	5	2
Nerve conduction	9	1	5	2	4-10	5	3
Pulsing	9	1	3	3.5	1-6	3	2

Table 4.2 Aggregate rating responses of importance for individual neuropathic pain symptoms, signs and investigations, expressed on a 0-10 numerical rating scale from participants in Delphi rounds 2 and 3.

QST = Quantitative Sensory Testing, n = number of responses, IQR = Interquartile range, ANP = Acute Neuropathic Pain

Important	Not Important
Spontaneous	Paroxysmal
Shooting	Pulsing
Burning	Radiology
Dysaesthesia	Nerve Conduction
Allodynia	
Hyperalgesia	
Difficult to manage pain	
Poor response to opioids	
Good response to antineuropathics	

Table 4.3 Neuropathic pain symptoms, signs and investigations achieving consensus after 3 Delphi rounds.

Cronbach's Alpha for the 9 items considered important and achieving consensus was 0.664. If item "spontaneous" was deleted, Cronbach's Alpha rises to 0.798. This item correlates poorly with the composite scores from the other items (corrected item-total correlation -0.303). Cronbach's Alpha for the 4 items considered not important and achieving consensus was 0.0. If item "Nerve conduction studies" was deleted, Cronbach's Alpha rises to 0.525. Cronbach's Alpha was also used for evaluating internal consistency among experts. Cronbach's Alpha for round 2 was 0.658 rising to 0.705 after round 3. The individual panelist-group correlations are presented in table 4.4. The panelist-group correlation increased in 7 out of 10 instances following round 3, corresponding to the higher Cronbach's Alpha observed.

| | Panelist-group correlation | |
Panelist	Round 2	Round 3
A	0.552	0.616
B	0.278	0.775
C	-0.041	-0.019
D	0.564	0.565
E	0.090	0.1
F	0.260	0.233
G	0.646	0.686
H	0.245	0.269
I	-0.057	-0.079
J	0.574	0.550

Table 4.4 Panelist-group correlations for Delphi rounds 2 and 3

4.5 Conclusion

This three round Delphi survey of acute pain specialists has identified a number of acute pain characteristics that may be important in aiding the diagnosis of acute neuropathic pain in the post-operative period. Importantly, it informs how specialists are diagnosing this problem in the absence of diagnostic criteria or robust research in this area.

Twenty-four items were identified by the first round "brainstorming" phase of the Delphi process, and agreement was achieved among specialists for 14 items, with 9 of these items identified as important. Although the majority of panelists did not change their scores between round 2 and 3, an improvement in Cronbach's alpha suggests an increase in homogeneity of opinion between Delphi rounds.

One interesting result of the Delphi process was the high level of consensus amongst panelists that response to medication plays an important role in

diagnosing neuropathic pain in the acute setting. The two items with the highest level of agreement (lowest IQR) were 'poor response to opioid analgesics' and 'good response to anti-neuropathic analgesics'. This contrasts markedly with the diagnosis of neuropathic pain in the chronic setting, where a prospective diagnosis of neuropathic pain is made on the basis of history, examination and investigation before appropriate drug therapy is used. Certainly, the empirical use of anti-neuropathic medications as a diagnostic (as well as therapeutic) aid in the acute post-operative setting probably reflects a pragmatic approach in light of the practical difficulties of using more established neuropathic pain diagnostic techniques. Using a poor response to opioids as a diagnostic aid is another interesting finding, and runs counter to the evidence of opioid efficacy in the chronic neuropathic pain population, where the NNT is less than more established anti-neuropathic treatments (such as gabapentin).[46]

Other symptoms achieving consensus as important items include the presence of dysaesthesias. Interestingly, question 1 of the LANSS relates to the presence of dysaesthesias, and was shown in chapter 3 to be the LANSS item most predictive of developing chronic neuropathic pain after surgery if present in the immediate post-operative period.

What is less clear is the role of autonomic symptoms or signs (such as colour change or swelling). Although the presence of these forms a part of existing neuropathic pain tools, the face validity of such items would appear to be lacking in the face of the normal inflammatory response to surgery, which can produce similar changes. Although the median scores of these items in the Delphi were relatively high, the range of results indicated little expert

consensus, with some clearly feeling these items are unimportant, and unwilling to change their minds.

Relying on confirmatory tests to aid the diagnosis of neuropathic pain may also be confounded by perioperative interventions (such as the use of local anaesthetics) and the availability of equipment (such as QST or electromyography), and the expert panel agreed that neither nerve conduction studies nor radiological investigations were useful diagnostic aids in a clinical setting.

It is important to note that although items with a median score <7 are considered not important in this study, care should be taken in inferring these items are not useful. There was a lack of internal consistency amongst the 4 items agreed to be not important. This may reflect the fact that the default definition of 'not important' actually contains a spectrum of responses ranging from those with a very low median score (such as 'pulsing' median=3) to those with borderline important scores ('paroxysmal' median=6). There is subsequent low correlation and covariance between the individual results.

The Delphi technique has a number of attractions when seeking to acquire agreement in areas of uncertainty or where there is lack of empirical evidence, and it has been previously used to facilitate the development of diagnostic criteria in the healthcare setting.[279, 303-306] It is important however, to understand the limitations and criticisms that can limit the usefulness of this type of consensus exercise.

4.5.1 Study limitations

There has been much debate over the validity of the Delphi technique since it was conceptualized in the post second world war period. Some commentators have argued that it fails to meet the standards required for scientific methodology, particularly in those studies with poor questionnaire design, reliability testing and selection of experts, with others describing it as a method of "last resort".[277, 307]

The expert panel chosen to participate in the Delphi technique is often cited as critical to the success of a project.[280] As the exact composition of the panel will affect the results obtained, the potential for bias in this aspect of Delphi methodology is considerable.

For this study, invitations to participate were sent to two groups: researchers who had published on the subject of acute neuropathic pain, and members of the British Pain Society Acute Pain Special Interest Group (SIG). Whilst authors of research in the area of acute neuropathic pain could be expected to be well informed on the topic, there is no guarantee that members of the Acute Pain SIG have knowledge on the topic. Furthermore, the BPS is a multidisciplinary society, therefore the panel invitation may be sent to doctors or nurses of varying experience and qualifications, and is no guarantee of expertise or familiarity with the topic in question.

Some Delphi studies have been able to apply rigorous selection criteria to expert panels. Keeney et al., (2011) cite examples from outside medicine, which required panelists to be academics with a record of published research on the topic in question in major journals.[280] While this may be practical in some

academic areas, the paucity of published research on the topic of acute neuropathic pain means this approach would not have been feasible.

One approach to improve the knowledge of the expert panel may have been to include background research reading as part of the Delphi exercise. This may have helped inform the panel about published research in this area, however, Raine et al., (2004) found that although providing a literature review improved concordance, if clinical experience and beliefs were not consistent with research evidence, then experience and beliefs seemed to take precedence.[308]

The adoption of the Acute Pain SIG membership as panel members presented a number of advantages. Membership implies a degree of active interest in acute pain, and members were easily contacted via the British Pain Society secretariat. The background hypothesis of the study was that clinicians working in the field of acute pain would have practical experience of diagnosing neuropathic pain in the acute post-operative period (as there is a paucity of published criteria to aid diagnosis), thus the most important pre-requisite for panel membership would be practical experience in the field of acute pain. Although data were incomplete, our results show a range of experience levels with half the original panelists having at least 5 years experience in acute pain.

In addition to the composition of the expert panel, size and rate of attrition are also considered important. Although 24 individuals answered at least one question in round 1, only 14 left contact details indicating a willingness to continue with the Delphi process and then only 10 completed round 2. The number of participants in the Delphi process should probably be at least 12, with less than six considered unreliable.[279] Less is known about acceptable

rates of attrition, with published studies varying between 8% and 100%.[280]

Some commentators have recommended a 70% response rate as necessary to maintain methodological rigor, although this is based on opinion rather than research in the area.[309, 310] Nevertheless, high attrition rates may result in bias and a potentially unrepresentative small sample.[280]

Anonymity is cited as a key feature of the Delphi method, providing the opportunity for each panel member to present and react to ideas without bias attributed to knowledge of the identities of other participants.[289] True anonymity requires both the researcher and panelists to be blind to the source of questionnaire responses.[311] Although Delphi panel members in the presented study were blind to the composition of the panel, the researcher aggregating the results and designing the subsequent questionnaire was not blind to the panel membership, introducing the potential for bias. This is a common pragmatic approach to performing Delphi studies, and has led to some authors dubbing the process "quasi-anonymity".[283, 312] It is not known what effect a lack of full anonymity has on Delphi findings.[313] Interestingly, anonymity has been cited as a weakness of the Delphi process, with concerns that some respondents do not engage with the process responsibly. In addition, the first round "brainstorming" process may be limited by the inability of participants to interact in the idea-generating phase.

A variety of techniques have been used to define consensus within the context of a Delphi study, with no guidelines or widespread agreement on the optimal methodology. This study used pre-determined levels of consensus based on the inter-quartile range, an approach common to other Delphi survey on diagnostic criteria.[304] Although the use of pre-determined levels of consensus

may be criticized, some authors have suggested it may reduce researcher bias by removing the temptation to manipulate results.[314]

Perhaps the most important limitation of the Delphi technique lies in the interpretation of a study's results. In particular, it is important not to equate consensus with validity: the existence of consensus does not mean the "correct" answer has been found.[277] Indeed, there is a danger that the process will identify collective bias or ignorance rather than wisdom.[277] Delphi is a means of identifying medical opinion, but is no substitute for conventional medical research. It can however, help to identify areas in which further research should focus. Pill (1971) recommends consensus results should be matched with observable events wherever possible.[315]

This Delphi survey identified items of possible diagnostic value in the area of acute post-operative neuropathic pain. Some of these items differ significantly to those found in conventional chronic neuropathic pain screening tools and diagnostic aids. The next stage of research presented in this thesis is to move towards confirmation of these results through observational study.

5 Are patients with poorly controlled postoperative pain more likely to have neuropathic symptoms and signs?

5.1 Introduction

The previous chapter reporting the results of a Delphi survey of diagnostic indicators of acute postoperative neuropathic pain suggested that two factors not used in the diagnosis of chronic neuropathic pain were considered useful in a clinical acute pain setting: difficult to control pain, and pain poorly responsive to opioids.

The validity of using these observations as useful diagnostic indicators of neuropathic pain is unclear, and arguments for and against this hypothesis can be made. For example, in a chronic pain setting, neuropathic pain responds well to opioids, which demonstrate a NNT lower than many established anti-neuropathic medications.[46] However, at a molecular level, raised levels of cholecystokinin (CCK), a hormonal peptide known to reduce the anti-nociceptive effects of opioids, occur within days of nerve injury and may be a mechanism for a poor response of neuropathic pain to strong opioids in the postoperative period.[316] In addition, there is evidence of reduced opioid binding sites in the dorsal horn of the spinal cord in the first two weeks after nerve injury.[317]

If patients with poorly controlled pain, which is not responsive to opioids are considered more likely to have acute neuropathic pain, they should also

demonstrate the presence of other symptoms and signs suggestive of neuropathic pain. This chapter presents a pilot study designed to evaluate neuropathic symptoms in patients with difficult to control pain after surgery, referred to the acute pain service.

It was hypothesized that patients with poorly controlled post-operative pain, unresponsive to opioids, have higher odds of developing other neuropathic symptoms, as suggested by expert opinion.

This chapter presents the results of a pilot cohort study. The specific aims of this pilot study were to report on the research processes that would be used in a larger study, including recruitment, questionnaire design, case matching methods and sample size calculation.

In a cohort study, exposure is identified before the outcome. Not only does this provide the potential to examine causality, but is particularly useful for examining rare exposures.[318] The disadvantages of cohort studies include the tendency to need large sample sizes that can result in costly or lengthy investigations, hence the usefulness of a pilot study that will allow accurate sample size calculations.[318]

5.2 Methods

Study outline

This pilot study was designed as a matched cohort investigation. Matched cohort studies have cases and controls relating to the exposure of interest (in this study difficult to control pain, poorly responsive to opioids), rather than the outcome of interest (occurrence of neuropathic symptoms).

This investigation sought to identify cases of patients following surgery with difficult to control pain, which has responded poorly to a standard analgesic regime based on opioids. Controls were identified from the postoperative population with well-controlled pain. Both groups were investigated with a questionnaire designed to elicit other neuropathic pain symptoms and signs based on the results of the previously presented Delphi survey and existing neuropathic pain screening tools. If difficult to control pain, that responds poorly to opioid analgesics is an indicator of acute neuropathic pain, the odds of developing other neuropathic symptoms and signs should be higher in this group compared to those with well controlled postoperative pain.

The study protocol was reviewed by the South West Regional Ethics Committee who deemed full ethics approval was not required for this questionnaire project.

5.2.1 Selection of cases and controls

Cases were identified from patients who received surgery at the Royal Cornwall Hospitals NHS Trust, and who were referred to the acute pain service with difficult to control postoperative pain, despite standard analgesic treatment with strong opioid analgesics (see appendix 6 'Criteria for referral to the Acute Pain

Service' and appendix 7 'Opioid treatment guidelines for the management of severe pain').

Difficult to control post-operative pain was defined as a pain score ≥4/10 on a numerical rating scale of pain intensity anchored 0 (no pain) and 10 (worst possible pain). This has been shown to correlate with moderate to severe pain in the post-operative period.[319] Standard analgesic treatment was defined as the use of oral, intravenous, intramuscular or subcutaneous strong opioid treatment (morphine or it's equivalent), in standard acute pain service protocol doses.

Patients were excluded if they were under the age of 18, pregnant, unable or unwilling to complete the study questionnaire. Additional exclusions aimed to reduce the number of patients with poorly controlled pain from other causes, and included: analgesia not given as prescribed, known pre-existing neuropathic pain, known pre-existing strong opioid use, and the use of epidural analgesia. Initially, recruitment was confined to the period 24-96 hours post surgery and patients with nerve plexus or peripheral nerve blocks were excluded.

This protocol was modified after 6 months. The recruitment timeframe of 24-96 hours postoperatively was extended to include patients after discharge from the recovery ward and up to 3 months after surgery. This would allow inclusion of patients referred to the acute pain service because of difficult to control pain during the rehabilitation phase of their recovery whilst still inpatients in the hospital. Patients who had received nerve blocks as part of their anaesthetic were also included (as discussed in the results section and conclusion).

A summary of the initial study design is presented in figure 5.1.
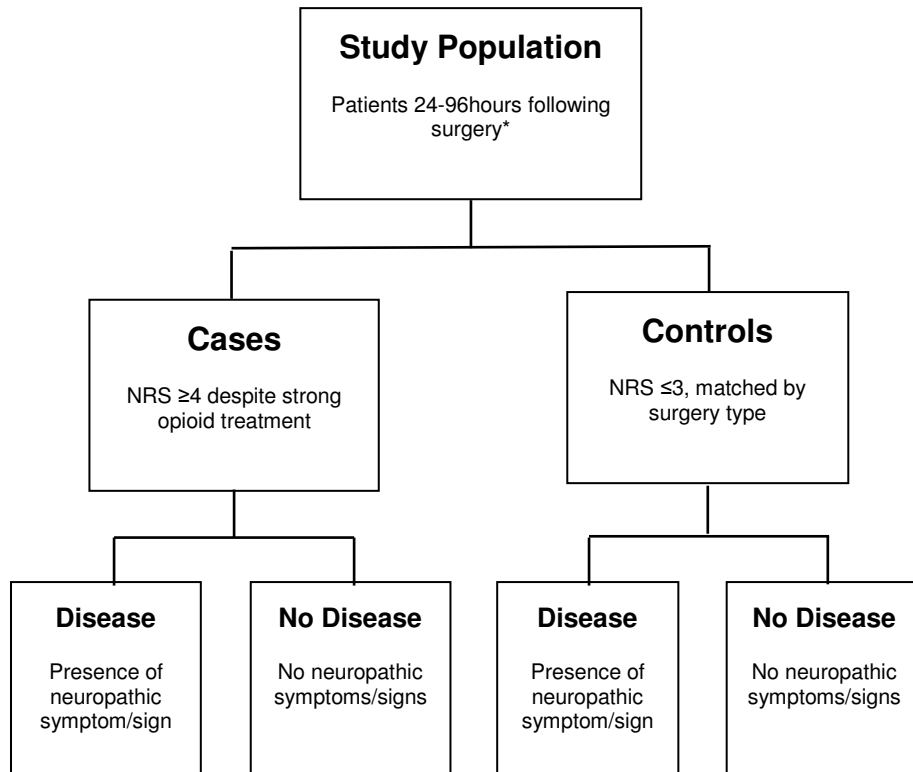
Figure 5.1 Study design for the matched cohort pilot evaluation of neuropathic symptoms and signs in patients with well controlled postoperative pain compared to those with poorly controlled postoperative pain.

NRS = Numerical Rating Scale of pain intensity (0-10)

* Following a protocol change after 6 months, this was extended to include patients within 3 months of surgery.

Controls were matched by surgery type. Matching cases to controls provides a way of controlling for known confounding variables. Although there is a paucity of research identifying risk factors for the development of acute neuropathic pain, there is good evidence that chronic neuropathic pain is more common following certain surgical procedures.[135] In the acute pain setting, surgery type is also likely to influence the development of neuropathic pain. In chapter 3, the incidence of acute neuropathic pain in the thoracic surgery population was 8%, twice that reported by patients undergoing elective general or orthopaedic surgery.[257] In their study of all patients referred to the acute pain service, Hayes et al., (2002) found that nearly half of all acute neuropathic pain diagnoses came from the traumatic injury population.[174] Type of surgery is therefore likely to be a significant confounding variable, and controls were therefore matched by surgical type. Ideally, control patients would be matched to the exact surgical procedure performed for each case. However, pragmatically, because of the individual nature of many operation types, particularly those performed for emergency or trauma reasons, this was not likely to be feasible. Instead, operations were coded according to operation site (e.g. upper limb), specialty (e.g. orthopaedic), and minor or major classification. Operation codes used are presented in table 5.1.

Patients with well-controlled pain, described as a pain intensity score of 3 or less on the same (0-10) numerical pain scale used to identify cases, were asked to complete the same questionnaire. The same exclusion criteria were applied to this group of patients. Patients in the control group were recruited at random having been initially identified by surgery type.

Operation	Example	Code
Upper abdominal minor	Laparoscopic cholecystectomy	1
Upper abdominal major laparoscopic	Nissen fundoplication	2
Upper abdominal major open	Pancreatectomy	3
Lower abdominal minor	Appendicectomy	4
Lower abdominal major laparoscopic	Hemicolectomy	5
Lower abdominal major open	Anterior resection	6
Gynaecological minor	Hysteroscopy	7
Gynaecological major laparoscopic	Laparoscopic oophorectomy	8
Gynaecological major open	Hysterectomy	9
Urology minor	Cystoscopy	10
Urology major	Nephrectomy	11
Abdominal wall	Hernia repair	12
Orthopaedic upper limb minor	K-wire to hand fracture	13
Orthopaedic upper limb major	Shoulder decompression	14
Orthopaedic lower limb minor	Knee arthroscopy	15
Orthopaedic lower limb major	Fractured femur	16
Orthopaedic pelvic	Fixation of pelvic fracture	17
Thoracic minor	Rigid bronchoscopy	18
Thoracic major	Thoracotomy	19
Cardiothoracic sternotomy		20
Breast minor	Augmentation/reduction	21
Breast major	Mastectomy	22
Plastics minor	Split skin graft	23
Plastics major	Reconstruction surgery	24
Maxillo-facial/ENT minor	Tonsillectomy	25
Maxillo-facial/ENT major	Neck dissection	26
Spinal minor	Discectomy	27
Spinal major	Fusion	28
Vascular abdominal major	Open aneurysm repair	29
Vascular lower limb minor	Varicose veins	30
Vascular lower limb major	Amputation	31
Vascular upper limb minor	Fistula formation	32
Vascular upper limb major	Amputation	33

Table 5.1 Operation codes and examples used when matching controls with cases in the matched cohort evaluation study.

ENT = Ear Nose and Throat surgery

5.2.2 Questionnaire design

From the Delphi survey presented in chapter 4, expert consensus concluded that 9 items were important in diagnosing acute neuropathic pain (table 14). The questionnaire design sought to incorporate 6 of these items: spontaneous, shooting, burning, dysaesthesia, allodynia and hyperalgesia. Where possible, questions relating to these symptoms were based on those already used in existing screening questionnaires, with known face validity and acceptability. The final questionnaire used is presented in appendix 8.

Question 1 is based on S-LANSS item 4, and is designed to elicit spontaneous pain.

Question 2 is based on S-LANSS item 5, and relates to the symptom of burning pain.

Question 3 investigates the presence of shooting pains.

Question 4 is designed to elicit the symptom of dysaesthesia, and is based on item 1 of the LANSS questionnaire.

Questions 5 to 8 are self examination items designed to elicit allodynia, hyperalgesia or sensory loss, adapted to the post-operative setting.

Additional data collection included analgesia used since the operation, planned analgesic use, operation type, number of hours or days post-surgery, demographic data and 0-10 numerical rating of pain intensity.

5.2.3 Statistical methods

Odds ratios for each questionnaire item were calculated. Odds ratios were estimated using conditional maximum likelihood estimates, and Fisher's exact

test of statistical significance (to account for the relatively low sample sizes). Demographic and treatment variables were examined for statistically significant differences. Fisher's exact test was used for categorical variables, and Mann Whiney U tests for continuous variables. Sample size calculations were performed for a prevalence of acute neuropathic pain of 8% (based on the findings presented in chapter 3), and for a range of neuropathic pain prevalence rates and odds ratios based on the results of the pilot study. Sample size calculations were performed based on the methods described by Wang et al., (2002).[320] Statistical advice and analysis was provided by Sarah Marley (statistical consultant).

5.3 Results

5.3.1 Study recruitment

In the 10-month period from July 2012 to May 2013, 24 cases were identified from referrals to the acute pain team at the Royal Cornwall Hospital, Truro. Twenty-one matched controls were identified by operation type. During the first six months of recruitment, only 8 cases were identified. In order to improve recruitment, the time period for recruiting cases was extended beyond 96 hours after surgery, and the exclusion criteria of peripheral nerve block was removed. Following changes to the protocol, in the four months from February to May 2013, a further 16 patients were recruited. No patients were recruited beyond 5 days after surgery.

5.3.2 Matched case controls

Details of the operations received by patients recruited to the pilot study are presented in table 5.2. Seventy one percent (n=15) of cases were major lower limb orthopaedic, 14% (n=3) were laparoscopic gynaecological cases, 10% (n=2) were major upper limb orthopaedic and 5% (n=1) were major laparoscopic lower gastro-intestinal surgery.

Case operation	Control operation	Operation code
Revision total knee replacement	Revision total knee replacement	16
Revision total knee replacement	Revision total hip replacement	16
Total knee replacement	Total knee replacement	16
Total knee replacement	Total knee replacement	16
Total knee replacement	Total knee replacement	16
Total knee replacement	Total knee replacement	16
Total hip replacement	Total hip replacement	16
Total hip replacement	Revision total hip replacement	16
Dynamic hip screws	Hip hemiarthroplasty	16
Revision total hip replacement	Revision total hip replacement	16
Resection of tibia	Femoral osteotomy	16
External fixation of ankle fracture	Open fixation of ankle fracture	16
Femoral nail	Open fixation of femoral fracture	16
Tibial nail	Revision total hip replacement	16
Ankle fusion	Patello-femoral replacement	16
Arthroscopic subacromial decompression of shoulder	Arthroscopic rotator cuff repair	14
Arthroscopic subacromial decompression of shoulder	Arthroscopic rotator cuff repair	14
Laparoscopic hysterectomy	Laparoscopic hysterectomy	8
Laparoscopic hysterectomy & oophorectomy	Laparoscopic hysterectomy	8
Laparoscopic oophorectomy and vaginal repair	Laparoscopic cystectomy	8
Laparoscopic ileocaecal resection	Laparoscopic hemicolectomy	5

Table 5.2 Operation details of the cases recruited to the matched cohort study, and their controls.

5.3.3 Questionnaire design

Analysis of the pilot data demonstrates some inconsistent responses to the examination items (questions 5 to 8). Patients answering 'yes' to question 5 ("The painful area feels no different from the non-painful area") should in theory answer 'no' to questions 6 to 8, which seek to elicit hyperalgesia, allodynia, or numbness.

The pilot data shows that 11 (46%) patients in the case group and 2 (8%) patients in the control group answered 'yes' to question 5, and then 'yes' to at least one other examination question eliciting different sensations to normal.

Incomplete data were present for 2 cases and 2 controls. All missing data related to one or more examination items. The two reasons given for incomplete data collection were an inability to examine the operative site (for example presence of a plaster cast), or the patient unwilling to touch the skin over the operated area.

5.3.4 Odds ratio calculations for individual questionnaire items

There is evidence (at the 5% level) that, compared to controls: Cases have a greater odds of suffering pain that comes on suddenly in bursts for no apparent reason, even when completely still (Q1); Odds ratio (OR) = 9.16; 95% Confidence Interval (CI) = (1.83, 64.38); p-value = 0.0036. Cases have a greater odds of experiencing pain feeling like strange unpleasant sensations in the skin (Q4); OR = 14.11; 95% CI = (1.62, 686.69); p-value = 0.0089. Cases have a greater odds of feeling discomfort like pins & needles, pricking or burning that is different from the non-painful area (Q6); OR = Inf; 95% CI = (1.68, Inf); p-value = 0.0086. Cases have a greater odds of the painful area

being more sensitive on examination than a non-painful area, (but not more sensitive than the patient had expected after surgery) (Q7); OR = 27.03; 95% CI = (4.35, 317.75); p-value < 0.0001. All of the other questions (except for Q5) have odds ratios greater than 1, but the results do not reach statistical significance. Results for each questionnaire item are presented in table 5.3.

Questionnaire Item	Cases* (N=)	Controls* (N=)	Odds Ratio	95% C.I.	P Value
1	13	3	9.16	1.83-64.38	0.0036[§]
2	7	2	4.58	0.72-51.74	0.13
3	9	3	4.34	0.85-30.09	0.0855
4	9	1	14.11	1.62-686.69	0.0089[§]
5	10	14	0.49	0.1-2.12	0.3332
6	7	0	Infinity	1.68-Infinity	0.0086[§]
7	16	2	27.03	4.35-317.75	<0.0001[§]
8	9	5	2.35	0.54-11.46	0.3264

Table 5.3 The number of patients answering each questionnaire item positively in the case and control groups of the matched cohort study, and the calculated odds ratios.

Number of patients answering item "yes", § Statistically significant result (p=<0.05), N = number of patients, C.I. = confidence interval

5.3.5 Summary statistics for demographic and treatment variables

Statistically significant differences were observed between cases and controls for the following variables: pain score (median cases=7, median controls=2; p<0.0001), number of hours post-operatively the assessment was performed (median cases=24, median controls=10; p=0.0083), current PCA morphine usage (cases=10(47.6%), controls=2(9.5%); p=0.0148), nerve block current usage (cases=7(33.3%), controls=0; p=0.0086). Results are presented in full in table 5.4.

Characteristic	Statistic	Case	Control	p-value
Sex	Male, n (%)	5 (23.8)	11 (52.4)	0.1109
	Female, n (%)	15 (71.4)	10 (47.6)	-
	Unknown, n (%)	1 (4.8)	0 (0)	-
Age	Median	55.5	72	0.1001
	Mean	54.35	65.14	-
Pain Score	Median	7	2	$<0.0001^{\S}$
	Mean	7.43	2.29	-
Emergency	Yes, n (%)	4 (19)	1 (4.8)	0.3433
	No, n (%)	17 (81)	20 (95.2)	-
Hours Post-op	Median	24	10	$0.0083^{\S}$
	Mean	29.71	21.43	-
Paracetamol	Current, n (%)	20 (95.2)	20 (95.2)	~1
NSAIDs	Current, n (%)	11 (52.4)	5 (23.8)	0.1109
PCA morphine	Current, n (%)	10 (47.6)	2 (9.5)	$0.0148^{\S}$
PCA fentanyl	Current, n (%)	2 (9.5)	1 (4.8)	~1
Oramorph/Oxycodone	Current, n (%)	9 (42.9)	11 (52.4)	0.7579
Tramadol	Current, n (%)	6 (28.6)	1 (4.8)	0.0931
I.M./S.C. Morphine	Current, n (%)	4 (19)	1 (4.8)	0.3433
I.V. Morphine bolus	Current, n (%)	0 (0)	0 (0)	~1
Ketamine	Current, n (%)	0 (0)	0 (0)	~1
Gabapentin	Current, n (%)	0 (0)	0 (0)	~1
Pregabalin	Current, n (%)	1 (4.8)	0 (0)	~1
TCA	Current, n (%)	1 (4.8)	0 (0)	~1
Nerve block	Current, n (%)	7 (33.3)	0 (0)	$0.0086^{\S}$
Regional anaes Catheter	Current, n (%)	1 (4.8)	0 (0)	~1

Table 5.4 Summary statistics for demographic and treatment variables of patients recruited to the matched cohort study

§ p<0.05, PCA (patient controlled analgesia), I.M (intramuscular), S.C. (subcutaneous), I.V (intravenous), TCA (tricyclic antidepressant, n= number of patients

5.3.6 Sample size calculations

Sample size calculations are provided for testing the equality of the odds of experiencing post-operative neuropathic pain for case and control patients. Three estimates of the prevalence of neuropathic pain in control subjects (8%, 10% and 14%), and three estimates of the odds ratio between cases and controls (3, 6 and 9) are given in table 5.5. These are based on the prevalence of acute neuropathic pain found in thoracic surgery patients (8%), the prevalence of patients answering "yes" to question 1 of the pilot study (14%) and a figure of 10% to reflect a conservative midpoint between the two. A 90% power and 5% significance level are assumed throughout.

Control Prevalence	Case Prevalence	OR	Power	Alpha	N (per group)	N (total)
8%	21%	3	90%	5%	171	342
10%	25%	3	90%	5%	143	286
14%	33%	3	90%	5%	112	224
8%	34%	6	90%	5%	59	118
10%	40%	6	90%	5%	50	100
14%	49%	6	90%	5%	40	80
8%	44%	9	90%	5%	38	76
10%	50%	9	90%	5%	33	66
14%	59%	9	90%	5%	27	54

Table 5.5 Sample size calculations for a fully powered matched cohort investigation of postoperative neuropathic symptoms and signs, based on the results of the pilot investigation.

OR = odds ratio, N = number of patients

5.4 Discussion

This pilot study reports on a number of research processes important to the success of the main case control cohort study. In addition, it gives an initial assessment of the primary outcome of the study: to determine if neuropathic symptoms and signs are more common in patients with poorly controlled post-operative pain that is unresponsive to opioids.

Preliminary analysis of the pilot data show that the odds of patients developing neuropathic symptoms and signs are much higher amongst patients with poorly controlled post-operative pain that is unresponsive to opioids, compared to those with well-controlled pain. In particular, questions 1, 4, 6 and 7 demonstrate statistically significant differences between the two groups with odds ratios between 9 and infinity. This points towards confirmation of the results of the Delphi survey indicating that poorly controlled post-operative pain unresponsive to opioids is an important indicator of acute neuropathic pain. Questions 1 and 4 refer to the presence of spontaneous pain and dysaesthesias, and questions 6 and 7 refer to the examination items testing for sensory abnormalities such as allodynia and hyperalgesia.

Interestingly, in this small sample, the prevalence of each neuropathic symptom or sign in the control group tended to be higher than would be expected by the previously published prevalence studies of acute neuropathic pain. More than 9% of control patients answered "yes" to five of the 7 neuropathic questionnaire items, compared to 3-8% of patients in other studies.[174, 257, 321] This suggests that in our control group the prevalence of neuropathic symptoms may be higher than previously reported, however, importantly the distinction must be made between the reporting of one neuropathic sensory descriptor and the

diagnosis of neuropathic pain. No single descriptor is pathognomic of

neuropathic pain, and validated screening tools rely on identifying a cluster of

characteristic symptoms/signs for their accuracy. In fact, if the prevalence of

individual neuropathic symptoms in the control group is compared to the

answers for each individual question of the LANSS (performed post-operatively

in thoracic surgery patients) in Chapter 3, the results are not too dissimilar

(table 5.6)

Pain descriptor	Control prevalence	Thoracic surgery prevalence
Dysaesthesias	14%	11%
Spontaneous	14%	20%
Burning	10%	17%
Allodynia	0%	4%

Table 5.6 Comparison of neuropathic symptom prevalence in the control group of the matched cohort investigation, and thoracic surgery population (from data presented in Chapter 3)

Recruitment was initially disappointing, and threatened the viability of both the

pilot and main study. After discussion with the acute pain team, two main

barriers to recruitment were identified: the 24-96 hours post-operation time

period for eligibility, and the exclusion of patients who had received nerve

plexus or peripheral nerve blocks at the time of operation. These criteria were

originally included to reduce the inclusion of patients with poorly controlled pain

for reasons other than a significant neuropathic component to their pain.

Without these criteria, there was concern that patients who had received a local

anaesthetic nerve block would be recruited in the transition period between the

nerve block wearing off and the establishment of other forms of analgesia. However, local anaesthetic nerve blocks are a common form of analgesia in our institution, and after discussion with the acute pain team, it was felt that a significant number of patients were being excluded from recruitment because they had received this form of analgesia. In addition, it was felt that the inclusion criteria "Standard opioid therapy used" meant patients would not be recruited before they had failed a trial of opioid therapy.

Additionally, the decision was made to extend the timeframe of recruitment to that of a common definition of acute pain – pain of less than 3 months duration. This would allow the acute pain team to recruit patients with delayed poor pain control after their operation, presenting whilst still inpatients after their surgery. Martinez et al., (2012) demonstrated that in the iliac crest bone harvest model, a proportion of patients develop neuropathic pain between 48 hours and 1 month after surgery.[258] The extended recruitment period would potentially allow inclusion of these patients.

Following these changes to the protocol, the rate of recruitment more than doubled. However, only 24 cases were identified during the 10-month recruitment period. This recruitment rate suggests a multicentre final study would be needed to ensure adequate case numbers within a reasonable timeframe. A multicentre study may improve the generalisability and validity of the final results by including a broader range of surgical procedures and approaches. In addition, the ability to compare data collected from different sites can improve the detection of errors or problems compared to single centre studies.[322] Multicentre studies do however require strict adherence to research protocols in order for the results to be meaningful. For example, in this case, a

multicentre cohort study would need strict inclusion criteria to ensure that each case has had an adequate trial of strong opioids, as acute pain service protocols and practice differ across hospitals.

This pilot study also demonstrated some potential problems with the questionnaire design. The examination items demonstrated inconsistencies in the way the questions were answered, with some patients reporting the site of pain feeling no different to a non operated area, then going on to report signs of sensory dysfunction. The most likely explanation for this result is that the questionnaire wording is sufficiently ambiguous to confuse those administering and completing the assessment. The questions were originally adapted from the LANSS and S-LANSS screening tools, however in the original form, patients have a choice of reporting the painful site as feeling normal or abnormal, they are not given the option of choosing both responses as in the pilot questionnaire.

A perhaps less likely explanation, although one that should be considered, is that both the operated site and the "non-painful area" patients are asked to use as a comparator, are exhibiting sensory changes in the post-operative period. As discussed in the initial chapter of this thesis, the process of central sensitization can be initiated by surgery, and can cause areas of secondary hyperalgesia extending beyond the site of surgical injury.[104, 123] Patients with central sensitization may also present with areas of allodynia and temporal summation, and in theory this may account for the seemingly inconsistent responses of some patients to the examination items of the questionnaire, particularly if these areas are remote to the original site of surgery.[122]

In this pilot study, cases were matched with controls undergoing similar surgery. Type of surgery was considered likely to be a confounding risk factor for the development of acute neuropathic pain, and frequency matching can ensure that cases and controls have the same distribution of operation types. This helps to remove any potential bias in the odds ratio estimates due to this confounding factor. Frequency matching can also add to the efficiency of the final study if an analysis stratified by operation type is performed.

Rather than matching by exact operation type, controls were identified by site, approach and major/minor surgical category. This was felt to be a pragmatic approach to recruiting controls, as many operations, particularly emergency or trauma cases require individualistic surgery that may not be repeated frequently enough to allow realistic control matching.

The disadvantage of matching controls in this way is the degree to which the confounding risk is eliminated from subsequent analysis. For example, can we assume that patients having a total knee replacement have a similar surgical risk of developing acute neuropathic pain to those undergoing total hip replacement? There is little direct evidence in the acute setting to show that this is not the case. In the chronic post-surgical pain setting the prevalence of neuropathic pain following knee and hip arthroplasty is similar (3.6% vs. 5.2%), and systematic reviews have combined the results of both procedures when reporting overall prevalence rates.[135, 268, 323] However, other surgical sites may show greater differences between exact operations, depending on the proximity of neural structures. For example, inguinal hernia repair and appendicectomy could be matched together, although operations in the groin are known to have a high incidence of chronic neuropathic pain.[135] In this pilot study, 38% of cases

had an exact match with operation type therefore although surgery as a confounding factor is likely to be reduced, it may not be removed completely.

Whilst there was no statistically significant difference in age or gender between the two cohorts in this pilot study, there were some important differences, which may have influenced the final results. There was a significant difference in the timing of assessments between the case and control groups, (mean of 30 and 21 hours respectively). The inclusion criteria for the study were changed from a relatively tight post-operative window (24-96 hours following surgery) to include patients from the immediate post-operative period to 3 months after surgery. Although this may have improved recruitment, it has introduced another possible confounding factor. Theoretically, a case presenting with poorly controlled pain 2 months after surgery could be matched with a control from 2 hours after their operation. This may influence the results as it seems a proportion of patients develop neuropathic pain sometime between the immediate postoperative period and 3 month follow-up.[258, 321] Although the differences in the cases and controls in the pilot study are not this extreme, it may be that in light of the revised inclusion criteria, patients should be matched according to time following surgery, particularly if there are significant outliers. Whilst this may seem attractive this does however present a potential problem for recruiting controls, as patients with well-controlled pain will be at home and therefore impossible to identify and recruit.

A further change in the protocol allowed patients to be recruited if they had received a peripheral nerve block. Interestingly, there was a significant difference in nerve block use between the case and control groups in the pilot study (33% vs. 0%). There are two potential issues with this result. The first is

that patients are being recruited in the transition period between the block wearing off and establishment of alternative analgesic techniques. The second is that neuropathic symptoms may be related to the block itself, for example a temporary neuropraxia from the injection at the time of operation. This remains a further limitation of the pilot study results.

The results of this pilot study point towards confirmation that patients with poorly controlled post-operative pain are more likely to experience pain symptoms and signs suggestive of neuropathic pain. However the study sample size is small and further investigation is needed with a fully powered study for these results to be confirmed.

6 General discussion and conclusion

Over the last thirty years there has been huge progress in the understanding of neuropathic pain, both in basic science and pathophysiology and in areas of diagnosis and treatment. Yet neuropathic pain is still thought of principally as a chronic disorder, with little focus on investigating neuropathic pain around the time of onset, in the acute phase. Perhaps this has been because many disease processes leading to neuropathic pain lack a definitive starting point, with insidious onset of symptoms, such as in diabetic peripheral neuropathy, the norm.

Surgery, in contrast, does have a definitive point of onset and offers the opportunity to study disease processes such as the development of pain from the initial putative cause. Chronic neuropathic pain is increasingly recognized as a major complication of surgery, with many studies reporting the prevalence of this problem ranging from less than 5% to greater than 50% after a variety of surgical procedures.[135] Yet little is known about the period between surgery and the development of chronic neuropathic pain i.e. the acute postoperative phase. This is surprising, as anecdotally, the existence of neuropathic pain in the acute postoperative period has been well documented over many years. In the 1970's and 1980's phantom limb pain following amputation, now considered a neuropathic pain condition, was reported to occur in the immediate postoperative period in up to 84% of patients.[324, 325] In the 1990's bodies such as The National Health and Medical Research Council (NHMRC) of Australia and the authors of review articles sought to highlight the issue of acute

neuropathic pain.[326, 327] However, not until 2002 was the first estimate of the prevalence of this problem published following a prospective audit of patients referred to an acute pain service.[174] Since then there has been comment on the problem, and case reports, but overall no further research investigating this area prior to the publication of the research presented in this thesis.[163, 165, 328]

Identification of acute neuropathic pain following surgery is important, as we know that despite advances in drug development and delivery, a third of patients still suffer moderate to severe acute pain following surgery, a proportion largely unchanged since the 1950's. Neuropathic pain is largely treated differently to nociceptive pain, and responds to medication such as the tricyclic antidepressants and gabapentinoids. It may be that a proportion of the one third of patients with poorly controlled postoperative pain have a neuropathic component that is unrecognized and undertreated. Identifying these patients opens new avenues for improving their pain management. Additionally, as acute neuropathic pain seems to be predictive of chronic neuropathic pain, it offers the opportunity to identify 'at risk' patients early in the disease process and explore disease-modifying interventions.

The concept of acute postoperative neuropathic pain has been lent credence by developments in our understanding of the basic science of pain pathophysiology. Following nerve injury, a cascade of complex neurobiological events occurs that may result in neuropathic pain. Many of these changes to the central and peripheral nervous system begin rapidly following nerve injury. For example, in animal models of spinal nerve ligation injury, dramatic up regulation of $Na_{v1.8}$ sodium channel proteins are apparent in distal nerves by day 2 following injury.[329] Similar rapid up regulation of $Na_{v1.3}$ sodium channels

occurs after nerve ligation, transection or constriction.[329] Both these sodium channels have been implicated in the development of neuropathic pain, and may be responsible for features such as 'spontaneous' pain.[329]

Another process implicated in the development of neuropathic pain is the activation of neuroimmune cells such as microglia following nerve injury. Microglia appear to have an important role in signaling to neurons in the dorsal horn, causing modulation of nociceptive processing. In particular, they may have a role in the development of hyperalgesia and allodynia after nerve injury.[330] Microglia show signs of activation 24 hours following nerve injury, with a peak in the proliferation of cells at 3 days, suggesting neuropathic symptoms may be possible within this timeframe following nerve injury.[330] Other changes to the central nervous system may also promote the early experience of neuropathic pain after surgery. Following nerve damage, the somatosensory cortex becomes reorganized, with inputs from the transected nerve expanding to three times the normal size within 1-2 days.[331] Cortical reorganization has been implicated in the development of phantom limb pain following amputation, which is known to occur in the immediate postoperative period.[332]

The focus of this thesis has been to expand scientific knowledge in the field of acute neuropathic pain following surgery. The research presented in this thesis has demonstrated that an existing screening tool for neuropathic pain (the LANSS) has important measurement properties in the chronic postoperative pain population.[241] It has estimated the previously unknown prevalence of acute neuropathic pain in thoracic surgery patients using this screening tool, and demonstrated a link with the development of chronic neuropathic pain 3 months later.[321] It has also explored how best to diagnose this problem, using

consensus methodology to gauge expert opinion and testing this in a clinical study with resulting identification of key diagnostic indicators of acute neuropathic pain.[333]

One of the key findings of the research presented in this thesis has been to give a plausible estimate of the prevalence of acute neuropathic pain in an at risk surgical population. Eight percent of thoracic surgery patients demonstrated pain of predominantly neuropathic origin using the LANSS questionnaire. Importantly, patients with pre-existing neuropathic pain were excluded from the study, so a direct causal link with surgery was established. The figure of 8% is interesting as evidence suggests that gabapentin, a drug used to manage neuropathic pain, and unlikely to be helpful in nociceptive pain, has an NNT of 11 when used in the postoperative period. It may be that the one in eleven patients benefitting from gabapentin in this scenario are experiencing a significant neuropathic component to their acute pain experience. In common with previous findings, this study also demonstrated a link between acute neuropathic pain and the development of chronic neuropathic pain. However, the LANSS screening tool, although demonstrated measurement level properties in the chronic postoperative pain population, was not designed to be used in the immediate postoperative period. The face validity of the tool in this context was questionable and therefore further exploration of factors likely to be indicative of acute neuropathic pain was warranted.

The Delphi survey of acute pain specialists identified some interesting neuropathic pain discriminators that are not typically used in the diagnosis of chronic neuropathic pain, but may be helpful in the acute pain setting. Pain that is poorly controlled by opioids has some scientific basis for indicating

neuropathic pain, as nerve damage is known to alter the balance of hormones and receptors in the central nervous system that could impair the antinociceptive effects of opioids. Cholecystokinin (CCK) levels in the central nervous system are raised within days of nerve injury and contribute to an impaired opioid response.[316] Opioid binding sites in the dorsal horn of the spinal cord are reduced within weeks of nerve injury.[317]

The pilot study presented in chapter 5 indicates that this hypothesis may well be true, demonstrating that neuropathic symptoms and signs seem to be much more common in patients with poorly controlled postoperative pain that does not respond well to opioids.

The field of neuropathic pain has seen significant change in the last 5 years, which has made research in this area challenging. For example, during the course of the research published in this thesis, the accepted definition of neuropathic pain has changed from "pain caused by damage or disruption of the nervous system" to "pain caused by a lesion or disease of the somatosensory nervous system".[2] Such changes are often controversial, and in this case led to confusion over whether or not to include conditions such as CRPS as neuropathic pain states. The implication for the research presented in this thesis was that the LANSS screening tool was validated using a cohort of patients that included those with CRPS.[194] The LANSS and self-report version (S-LANSS) were used as screening tools to estimate the prevalence of acute and chronic neuropathic pain in the thoracic surgery population in chapter 3, although this study was performed prior to the change in neuropathic pain definition.

Not only has the definition of neuropathic pain changed during the course of this thesis, but also diagnostic criteria. A grading system for neuropathic pain was published by a body of experts in 2008, and was rapidly adopted by both the European Federation of Neurological Societies (EFNS) and the International Association for the Study of Pain (IASP).[138, 179] This grading system proposed three levels of diagnostic certainty for neuropathic pain based on four criteria. If patients have pain in a neuro-anatomically plausible distribution, and a history of a relevant lesion or disease they have "possible" neuropathic pain. If they also demonstrate either confirmatory tests of positive (hyperalgesia, allodynia) and negative (hypoalgesia, hypoaesthesia) signs in the innervation territory of the damaged nerve, or confirmatory diagnostic tests (such as MRI or nerve conduction studies), they have "probable" neuropathic pain. If they have all these criteria they have "definite" neuropathic pain.[138]

One problem with this grading system is a lack of clarity about which or how many sensory abnormalities are required to fulfill the criteria of neuropathic pain diagnosis. Further unanswered questions surround the role of verbal descriptors of neuropathic pain, which have played an important part in the development of neuropathic screening tools over the last ten years, yet do not play a part in the new grading system.

Using the new grading system to diagnose acute neuropathic pain would be challenging. Sensory abnormalities around operative wounds are common, with positive signs (such as hyperalgesia) resulting from peripheral sensitization of nociceptors, and negative signs (such as hypoaesthesia) resulting from local anaesthetic use. Similarly, the logistics, availability and reliability of confirmatory tests such as EMG, nerve conduction studies and MRI are questionable in a

clinical setting. Although nerve conduction studies at the time of operation revealed nerve damage is common during thoracic surgery, there is no correlation with sensory abnormalities or pain 3 months later.[66] Similar questions have been raised regarding the predictive qualities of MRI scanning. In patients with known lumbar disc herniation and sciatica, MRI findings do not correlate with pain symptoms at 1 year follow up.[334]

In contrast to this approach to diagnosing neuropathic pain, one feature of the research presented in this thesis has been the value of verbal descriptors of neuropathic pain in the acute postoperative setting. The verbal description of dysaesthesia for example, scored very highly for importance (median 9/10) when acute pain experts are asked what they consider to be useful in the diagnosis of acute neuropathic pain. The presence of dysaesthesia in the immediate postoperative period was more predictive of the development of chronic neuropathic pain than any other symptom or sign of the LANSS, or indeed the total LANSS score in thoracic surgery patients (odds ratio 12.6 versus 7.7 for a positive LANSS score). Similarly, the verbal description of dysaesthesia is far more common in patients with poorly controlled postoperative pain (that responds poorly to opioids) compared to those with well-controlled pain (odds ratio 14).

Other verbal descriptors identified in this thesis as potentially useful indicators of acute neuropathic pain include spontaneous, burning and shooting pain. Patients with spontaneous pain have a significant odds ratio (3.4) for the development of chronic neuropathic pain, and spontaneous pain is more likely to be present in patients with poorly controlled pain in the postoperative period (odds ratio 9.16). There is a trend towards burning and shooting pain being

more common in patients with poorly controlled postoperative pain, although the odds ratios (4 for both) were non-significant. Similarly, the predictive qualities of burning pain for the development of chronic neuropathic pain were non-significant (odds ratio 3).

The usefulness of verbal descriptors may extend beyond their diagnostic qualities, with limited evidence that they may predict response to analgesic medication.[192]

In contrast to the results of verbal descriptors of pain, the limited bedside examination items examined in this thesis demonstrated less clear evidence of usefulness. Whilst the presence of allodynia and hyperalgesia were much more common in patients with poorly controlled postoperative pain (odds ratio infinity and 27 respectively) and were considered important by the consensus panel of experts, they had the lowest predictive value for the development of chronic neuropathic pain in the thoracic surgery group, with non-significant odds ratios of 1.2 and 2.2 respectively.

Importantly, the LANSS item related to the presence of hyperalgesia can also be positive if hypoaesthesia is present (raised or lowered pin-prick threshold), and this may be a confounding factor between the study results in this thesis. Certainly, other authors have subsequently found that the area of secondary hyperalgesia around a wound in the postoperative period is related to the development of chronic postoperative pain, whereas hypoaesthesia is not.[258] This may account for the lack of predictive qualities of LANSS item 7 which can be scored positively in the presence of both hyperalgesia and hypoaesthesia. The results of Martinez et al., (2012) showing hypoaesthesia is not predictive of

the development of chronic postoperative pain is interesting in light of the results presented in chapter 5, which also show that the presence of numbness (question 8), although more common in the group with poorly controlled pain, is not significantly so compared to controls.

These results are consistent with the finding that evidence of nerve damage elicited with quantitative sensory testing is present in both those with chronic postoperative pain, and those without pain. QST in this scenario fails to differentiate between pain free and pain present patients following hernia repair and mastectomy.[273, 274] This points towards the observation that chronic postoperative pain does not develop in many patients despite significant sensory abnormalities. The research presented in chapter 3, showing a lack of the predictive value of the LANSS examination items supports this hypothesis and demonstrates this is true specifically for the development of chronic neuropathic pain.

The results presented in this thesis suggest that verbal descriptors of neuropathic pain may have a useful role to play in the diagnosis of acute neuropathic pain, in contrast to the direction of neuropathic pain diagnosis taken in recent years by IASP and EFNS. In addition to verbal descriptors, pain that is poorly controlled despite the use of strong opioids may indicate a group of patients at risk of neuropathic pain in the postoperative period.

A number of areas of further work are needed to help identify and define acute neuropathic pain. The results of the pilot study presented in chapter 5 need to be confirmed with a properly powered multi-centered study. Ideally, work should focus on developing diagnostic criteria for acute neuropathic pain, and

validating these against a gold standard. This would allow accurate measurement of the prevalence of acute neuropathic pain across surgery types. Unfortunately, the current gold standard for neuropathic pain diagnosis has moved away from using verbal descriptors and requires the use of confirmatory tests that elicit positive or negative sensory signs or confirm nerve lesion or disease. Quantitative sensory testing (QST) has become a popular way of detecting sensory abnormalities, typically testing mechanical pain thresholds to pinprick and pressure, mechanical detection thresholds to vibration and pinprick, hot/cold thresholds, allodynia and pain summation. QST protocols are available, and normal values have been described.[335] However, little information is available to describe normal sensory changes in wounds immediately after surgery, or the time course of changes in sensory abnormalities. Before complex sensory testing can be used as a confirmatory step in the diagnosis of acute neuropathic pain, the 'normal' changes that occur after surgery need to be described, and this presents a further potential area of study although the feasibility of this approach would need to be tested. In particular, the acceptability of performing these sorts of examinations in the early postoperative period may be questioned, as well as more practical concerns such as the risk of introducing infection to wounds and the need to remove dressings or even plaster casts.

The proportion of patients experiencing moderate to severe postoperative pain has remained remarkably static at 30% over the last 50 years, despite advances in our knowledge and understanding of nociceptive pain physiology and developments in the effectiveness and delivery of strong opioid analgesics and other forms of analgesia. One reason for this may be that we are under

recognizing and treating neuropathic pain in the immediate postoperative period. Neuropathic pain on the whole responds well to anti-neuropathic pain medications such as Amitriptyline or Gabapentin. If we use medications such as gabapentin on everyone in the postoperative period we know that the proportion of patients who gain benefit is small compared with more traditional acute pain analgesics, and the risk of unpleasant side effects considerable. The answer may therefore lie in identifying and treating those with acute neuropathic pain, rather than the majority with predominantly nociceptive pain after surgery. The difficulty has been identifying this small proportion of patients in the face of significant confounding factors, however this thesis has helped to advance knowledge in this area with the hope that this knowledge can be used to help develop diagnostic criteria or guidelines for acute neuropathic pain in the future

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Appendices

Appendix 1: The LANSS neuropathic pain screening tool

THE LANSS PAIN SCALE
Leeds Assessment of Neuropathic Symptoms and Signs

NAME_____ DATE_____

This pain scale can help to determine whether the nerves that are carrying your pain signals are working normally or not. It is important to find this out in case different treatments are needed to control your pain.

A. PAIN QUESTIONNAIRE

- Think about how your pain has felt over the last week.
- Please say whether any of the descriptions match your pain exactly.

1) **Does your pain feel like strange, unpleasant sensations in your skin? Words like pricking, tingling, pins and needles might describe these sensations.**

   a) NO - My pain doesn't really feel like this.................................... (0)

   b) YES - I get these sensations quite a lot.................................... (5)

2) **Does your pain make the skin in the painful area look different from normal? Words like mottled or looking more red or pink might describe the appearance.**

   a) NO - My pain doesn't affect the colour of my skin.................. (0)

   b) YES - I've noticed that the pain does make my skin look different from normal .... (5)

3) **Does your pain make the affected skin abnormally sensitive to touch? Getting unpleasant sensations when lightly stroking the skin, or getting pain when wearing tight clothes might describe the abnormal sensitivity.**

   a) NO - My pain doesn't make my skin abnormally sensitive in that area.......... (0)

   b) YES - My skin seems abnormally sensitive to touch in that area.................... (3)

4) **Does your pain come on suddenly and in bursts for no apparent reason when you're still. Words like electric shocks, jumping and bursting describe these sensations.**

   a) NO - My pain doesn't really feel like this .... (0)

   b) YES - I get these sensations quite a lot.................................... (2)

5) **Does your pain feel as if the skin temperature in the painful area has changed abnormally? Words like hot and burning describe these sensations**

   a) NO - I don't really get these sensations.................................... (0)

   b) YES - I get these sensations quite a lot .... (1)

B. SENSORY TESTING

Skin sensitivity can be examined by comparing the painful area with a contralateral or adjacent non-painful area for the presence of allodynia and an altered pin-prick threshold (PPT).

1) ALLODYNIA

Examine the response to lightly stroking cotton wool across the non-painful area and then the painful area. If normal sensations are experienced in the non-painful site, but pain or unpleasant sensations (tingling, nausea) are experienced in the painful area when stroking, allodynia is present.

a)   NO, normal sensation in both areas _____ (0)

b)   YES, allodynia in painful area only .... (5)

2) ALTERED PIN-PRICK THRESHOLD

Determine the pin-prick threshold by comparing the response to a 23 gauge (blue) needle mounted inside a 2 ml syringe barrel placed gently on to the skin in a non-painful and then painful areas.

If a sharp pin prick is felt in the non-painful area, but a different sensation is experienced in the painful area e.g. none / blunt only (raised PPT) or a very painful sensation (lowered PPT), an altered PPT is present.

If a pinprick is not felt in either area, mount the syringe onto the needle to increase the weight and repeat.

a)   NO, equal sensation in both areas .... (0)

b)   YES, altered PPT in painful area .... (3)

SCORING:

Add values in parentheses for sensory description and examination findings to obtain overall score.

TOTAL SCORE (maximum 24) ....

If score < 12, neuropathic mechanisms are **unlikely** to be contribution to the patient's pain

If score ≥ 12, neuropathic mechanisms are **likely** to be contributing to the patient's pain

Appendix 2: The S-LANSS neuropathic pain screening tool

APPENDIX

THE S-LANSS PAIN SCORE

Leeds Assessment of Neuropathic Symptoms and Signs (self-complete)

NAME_____   DATE_____

- This questionnaire can tell us about the type of pain that you may be experiencing. This can help in deciding how best to treat it.

- Please draw on the diagram below where you feel your pain. If you have pain in more than one area, only shade in the one main area where your worst pain is.
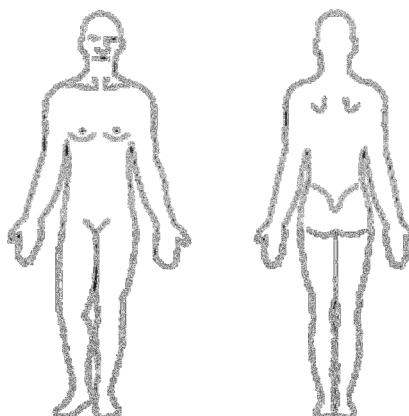
- On the scale below, please indicate how bad your pain (that you have shown on the above diagram) has been in the last week where:
  "0" means no pain and "10" means pain as severe as it could be.

NONE 0   1   2   3   4   5   6   7   8   9   10 **SEVERE PAIN**

- On the other side of the page are 7 questions about your pain (the one in the diagram).

- Think about how your pain that you showed in the diagram has felt over the last week. Please circle the descriptions that best match your pain. These descriptions may, or may not, match your pain no matter how severe it feels.

- Only circle the responses that describe your pain. **Please turn over.**

S-LANSS

1. In the area where you have pain, do you also have 'pins and needles', tingling or prickling sensations?

   a) NO – I don't get these sensations   (0)

   b) YES – I get these sensations often   (5)

2. Does the painful area change colour (perhaps looks mottled or more red) when the pain is particularly bad?

   a) NO – The pain does not affect the colour of my skin   (0)

   b) YES – I have noticed that the pain does make my skin look different from normal   (5)

3. Does your pain make the affected skin abnormally sensitive to touch? Getting unpleasant sensations or pain when lightly stroking the skin might describe this.

   a) NO – The pain does not make my skin in that area abnormally sensitive to touch   (0)

   b) YES – My skin in that area is particularly sensitive to touch   (3)

4. Does your pain come on suddenly and in bursts for no apparent reason when you are completely still? Words like 'electric shocks', jumping and bursting might describe this.

   a) NO – My pain doesn't really feel like this   (0)

   b) YES – I get these sensations often   (2)

5. In the area where you have pain, does your skin feel unusually hot like a burning pain?

   a) NO – I don't have burning pain   (0)

   b) YES – I get burning pain often   (1)

6. Gently <u>rub</u> the painful area with your index finger and then rub a non-painful area (for example, an area of skin further away or on the opposite side from the painful area). How does this rubbing feel in the painful area?

   a) The painful area feels no different from the non-painful area   (0)

   b) I feel discomfort, like pins and needles, tingling or burning in the painful area that is different from the non-painful area   (5)

7. Gently <u>press</u> on the painful area with your finger tip then gently press in the same way onto a non-painful area (the same non-painful area that you chose in the last question). How does this feel in the painful area?

   a) The painful area does not feel different from the non-painful area   (0)

   b) I feel numbness or tenderness in the painful area that is different from the non-painful area   (3)

Scoring: a score of 12 or more suggests pain of predominantly neuropathic origin

Appendix 3: Acute Neuropathic Pain Survey – Background Information

Background

This project is a web-based survey of expert opinion regarding the importance of different symptoms and signs in diagnosing acute neuropathic pain. Diagnosing neuropathic pain in the immediate post-operative period is challenging because of concurrent nociceptive pain from tissue damage, and a lack of published diagnostic criteria. Establishing a consensus on what symptoms and signs are important in diagnosing acute neuropathic pain will help inform future studies on the prevalence of this condition.

Delphic survey methods

The Delphic technique seeks to obtain consensus on the opinions of experts through a series of structured questionnaires. Experts complete the questionnaires anonymously, and the responses from each questionnaire are fed back in summarized form to the participants. The experts are then able to modify their individual responses in light of the group result. The initial questionnaire will generate a list of possible symptoms and signs, and in subsequent rounds, participants will be asked to rate the importance of these symptoms and signs on a 0 to 10 scale. Consensus is usually achieved after 2 or 3 survey rounds.

What will happen to the results?

All individual results will be anonymised before being analysed. Individual responses will not be attributable in any report or publication. The list of important symptoms and signs generated by the Delphic survey will be used in the design of a prospective observational study investigating the prevalence of these symptoms among the surgical population.

Appendix 4: Round 1 Delphi questions.

1. What symptoms are important in the diagnosis of acute neuropathic pain in the immediate post-operative period?

2. What clinical signs are important in the diagnosis of acute neuropathic pain in the immediate post-operative period?

3. What investigations are useful in diagnosing a significant neuropathic element to post-operative pain?

4. Do you use any other clinical tools to help diagnose acute neuropathic pain (e.g. screening questionnaires)?

5. Please specify which tools you use

6. What are the obstacles to diagnosing acute neuropathic pain in the immediate post-operative period?

7. How long have you been involved in acute pain management at consultant level?

8. Do you use anti-neuropathic pain medication in the immediate post-operative period?

9. How often do you use anti-neuropathic pain medication in the immediate post-operative period?

10. How do you decide when to use anti-neuropathic pain medication in the immediate post-operative period?

11. Which type of anti-neuropathic medication do you use in the immediate post-operative period?

Appendix 5: Round 2 Delphi questions

1. How important to you are the following symptoms in diagnosing acute neuropathic pain (on a 0-10 scale where 0=completely unimportant and 10=extremely important)?

    - Paroxysmal nature

    - Spontaneous nature

    - Sharp

    - Shooting

    - Pulsing

    - Stabbing

    - Lancinating

    - Burning

    - Pins and needles sensations

    - Dysaesthesias

2. How important to you are the following signs in diagnosing acute neuropathic pain (on a 0-10 scale where 0=completely unimportant and 10=extremely important)?

    - Changes in skin colour

    - Pain in an area of altered skin sensation

    - Allodynia

    - Hyperalgesia

    - Hyperpathia

    - Signs of autonomic dysfunction

3. How important to you are the following responses to acute pain management in diagnosing acute neuropathic pain (on a 0-10 scale where 0=completely unimportant and 10=extremely important)?

- Difficult to manage pain

- Poor response to Opioids

- Good response to trial of anti-neuropathic agents

- Good response to intravenous lidocaine

4. How useful to you are the following tests in diagnosing acute neuropathic pain (on a 0-10 scale where 0=completely useless and 10=extremely useful)?

- Neuropathic pain screening tools (e.g. the LANSS)

- Quantitative sensory testing

- Radiographic imaging (e.g. MRI)

- Nerve conduction studies

Appendix 6: Criteria for referral to the Acute Pain Service

Taken from "The Royal Cornwall Hospital Pain Services Referral Guideline" April 2012.

Pain should be measured using the verbal descriptor or categorical scale:

S = Sleeping

0 = No pain

1 = Mild pain

2 = Moderate pain

3 = Severe pain

Patients whose pain scores are persistently 2 or 3 (moderate or severe) despite the regular administration of appropriate analgesia should be referred for specialist pain advice.

Additional Acute Pain Service referral guidelines for post-operative pain:

- Pain control problem despite the regular administration of appropriate analgesia.
- Pain score regularly 2 or more on MEWS (modified early warning score) chart.
- Pain not controlled with specific mode of analgesia (PCA/epidural/intrathecal).
- Equipment concerns.
- Unwanted side effects.
- Medical/healthcare team request advice.

Appendix 7: Opioid treatment guidelines for the management of severe pain

Taken from The Royal Cornwall Hospital "Analgesic advice for ward doctors" version 1.

Pain Score

S   sleep
0   no pain
1   mild pain
2   moderate pain
3   severe pain

Patient with severe pain Unrelieved by appropriate dose of oral medication or post op local anaesthetic blocks

Sedation Score

0   awake
1   dozing intermittently
2   mostly sleeping
3   Difficult to rouse

Consider intravenous morphine – 10mg diluted in 0.9% saline to 10 ml (1mg/ml)
Ensure that respiratory rate>8 breaths/min and sedation score < 2.
Ensure intravenous access and administer iv morphine 2mg

Monitor resp rate and sedation score to maintain at resp rate>8/min and sedation 1-2
For 5 minutes.

If still in pain, repeat 2mg bolus at 5 min intervals maintaining stable observations to a .maximum dose of 20mg.

If now stable prescribe regular im morphine at 0.15mg/kg
At 1-2 hrly intervals overnight and review mane.
If pain still requiring regular hourly opiates contact acute pain team

If site manager able to set up PCA then prescribe:
Morphine 50mg in 50 ml, 1mg bolus and 5 minute lockout. and maintain with this

If there is an epidural in situ which is ineffective despite maximum infusion rate, seek anaesthetic advice or turn off and give iv morphine as above

Respiratory rate and sedation scores should be monitored at hourly intervals

The equivalent oral dose of morphine to 10mg iv is 20- 30mg oromorph
The equivalent im dose of morphine to 10mg iv is - 15mg morphine

Respiratory Depression - < 8 breaths/min
Mix 400mcg naloxone with 3 mls 0.9% NaCl – 100mcgms /ml
Give in 1 ml increments every 5 mins to Achieve resp rate>8/min and sedation score <2.

If you are unable to control pain after the above measures seek advice from the anaesthetist on call.

Appendix 8: Matched cohort study questionnaire

Please take a moment to help us improve how we assess pain after operations. Complete the following questions about how your pain has felt since your operation.

Please rate the pain you feel now on the scale below. 0 means no pain and 10 means pain as severe as it can be.

No pain   0   1   2   3   4   5   6   7   8   9   10   Severe pain

1. Does your pain come on suddenly in 'bursts' for no apparent reason, even when you are completely still?

☐ Yes

☐ No

2. In the area where you have pain, does your skin feel unusually hot, like a burning pain?

☐ Yes

☐ No

3. Do you experience 'shooting' pains?

☐ Yes

☐ No

4. Does your pain feel like strange unpleasant sensations in your skin? Pricking, tingling, pins & needles might describe these sensations.

☐ Yes

☐ No

Gently stroke the skin over the painful area, then stroke a non painful area (for example the opposite side of your body to the painful area). Now answer the following questions:

5. The painful area feels no different from the non-painful area?

☐ Yes

☐ No

6. I feel discomfort like pins & needles, pricking or burning that is different from the non-painful area.

☐ Yes

☐ No

7. The painful area is more sensitive than the non-painful area, but what I had expected after my operation.

☐ Yes

☐ No

8. The painful area feels more numb compared to the non-painful area?

☐ Yes

☐ No

To be completed by the pain nurse or doctor:

Date:

Inclusion Criteria

- Pain score ≥4/10
- Standard opioid therapy used (IV/IM/SC/PO morphine or PCAS)
- <3 months from time of operation

Exclusion Criteria

- Age under 18
- Unable or unwilling to participate
- Pregnant
- Known pre-existing neuropathic pain
- Known pre-existing strong opioid use (before hospital admission)
- Epidural

Patient sticker/Name & DOB

No. of hours/days Post-op

Operation

Analgesia used since operation

NSAIDS ☐

PARACETAMOL ☐

PCAS ☐

ORAMORPH ☐

IM/SC MORPHINE ☐

NERVE BLOCK ☐

OTHER:

Analgesic Plan

KETAMINE ☐

PREGABALIN ☐

GABAPENTIN ☐

AMITRIPTYLINE ☐

OTHER: