Epidemiology of neuropathic pain in primary care patients consulting with low back-related leg pain

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Declaration

This research in this thesis was nested in a prospective observational cohort study called the Assessment and Treatment of Leg pain Associated with the Spine (the ATLAS study) which was carried out at the Arthritis Research UK Primary Care Centre, Keele University. The idea for this study was developed by Dr Kika Konstantinou and Professor Kate Dunn who were both members of the main ATLAS research team and Professor Nadine Foster.

The objectives for the thesis were developed by myself with the support of my supervisors, Kika Konstantinou, Kate Dunn, Dr Reuben Ogollah (statistical advisor) and Nadine Foster. I planned and conducted all the statistical analysis presented in this thesis with support and advice from my supervisors and in particular Reuben Ogollah. My supervisors gave advice and feedback on the writing in the chapters and on presentation of the data.

I undertook formal training in statistics and statistical software in advance of carrying out the statistical analysis by attending MSc Advanced Quantitative Data Analysis module (multivariable analysis) at Keele University and Stata Summer School (advanced data management, graphics and medical statistics) held at CASS Business School, London. I attended formal epidemiology training at the UK Research in Musculoskeletal Epidemiology (UK-RIME) partnership Advanced Musculoskeletal Epidemiology Summer School (longitudinal analysis, missing data, pharmacoepidemiology) held in Manchester and at the PROGRESS Summer School in prognosis research, Keele. The work in this thesis relates to an Education and

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Joanne Jordan and Dr Opeyemi Babatunde advised on searching strategies for the systematic review. Dr Siobhán Stynes independently reviewed abstracts, Siobhán Stynes, Kika Konstantinou and Kate Dunn independently reviewed full-texts and assisted with quality assessment of studies in the systematic review. Sarah Lawton facilitated the collection of data and Jenny Titley collected data from general practice electronic medical and prescribing records. Dr Julie Ashworth provided clinical advice on prescribing patterns of pain medications in primary care.

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Abstract

Neuropathic pain (pain caused by nerve damage) is considered challenging to manage. One of the most common neuropathic pain conditions is believed to be the presence of sciatica in low back-related leg pain (LBLP). A systematic review of the literature highlighted a paucity of evidence on the prevalence, characteristics and prognosis of LBLP patients with neuropathic pain in primary care. Epidemiological analysis used an existing prospective cohort (n=609) of LBLP patients consulting in primary care, including items from routine clinical examination and self-report at baseline, plus general practice electronic medical and prescribing records of patients with neuropathic pain. Cases of neuropathic pain were identified using three definitions, two based on clinical examination (with or without MRI), and one using the self-report Leeds Assessment for Neurological Symptoms and Signs (s-LANSS). Prevalence estimates varied from 48% to 74% according to definition. At baseline, patients with neuropathic pain (across three definitions) had higher leg pain intensity, poorer pain self-efficacy, more had pain below the knee and sensory loss based on findings from routine neurological examination. The clinical course (pain intensity and LBLP-related disability) of patients with neuropathic pain rapidly improved up to four months after initial consultation; the extent of improvement depended on case definition. The presence of neuropathic pain changed over time, remaining persistent in 16% over three years. The clinical course of patients with persistent neuropathic pain was worse compared to those with non-persistent neuropathic pain; there was no evidence that neurological examination items were associated with persistent neuropathic pain at

four months. Pain medication was commonly prescribed to patients with neuropathic pain; 30% were prescribed neuropathic pain medication, patients improved with and without such medication. This thesis provides new evidence that challenges some commonly held perceptions about neuropathic pain, with clear implications for clinical practice and future research.

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List of Abbreviations

ATLAS	Assessment and Treatment of Leg pain Associated with the Spine Study
CI	Confidence interval (95%)
BMI	Body mass index (Kg/m^2)
GP	General Practitioner
HADS	Hospital Anxiety and Depression Scale
IASP	International Association for the Study of Pain
IPQ-R	Musculoskeletal Illness Perceptions Questionnaire
MRI	Magnetic Resonance Imaging
MRR	Medical Records Review
N	Number
NeuPSIG	Neuropathic Pain Special interest Group of IASP
NICE	The National Institute for Health and Care Excellence
NSAID	Non-steroidal anti-inflammatory medication
NHS	National Health Service
NRS	Numerical rating scale
OR	Odds ratio
PSEQ	Pain Self-Efficacy Questionnaire
RMDQ	Roland Morris Disability Questionnaire
SD	Standard deviation
s-LANSS	Self-report version of Leeds Assessment of Neuropathic Symptoms and Signs

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Research articles

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Work presented

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Harrisson, S. A. Ogollah R. Dunn, K. M. Foster, N. E. Konstantinou, K. Low back-pain related leg pain patients in primary care: Identifying change in the presence of neuropathic pain. XV International Back and Neck Pain Forum, Oslo, September 2017.

Harrisson, S. A. Ogollah R. Dunn, K. M. Foster, N. E. Konstantinou, K. Is the clinical course of patients with low back-related leg pain with neuropathic pain worse compared to those without? 6th International Congress on Neuropathic pain, Gothenburg, June 2017.

Harrisson, S. A. Change in the presence of neuropathic pain over time in patients with low back related leg pain consulting in primary care. Keele University Research Institute of Primary care and Health Sciences Postgraduate Symposium, May 2017.

Harrisson, S. A. Is the clinical course of patients with low back-related leg pain with neuropathic pain worse compared to those without? Keele University Institute for Liberal Arts and Sciences: Crossing paths conference, April 2017.

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Harrisson, S. A. Stynes, S. Dunn, K. M. Foster, N. E. Konstantinou, K. Neuropathic pain in primary care patients with low back and leg pain: prevalence, characteristics and prognosis. A systematic review of the literature. XIV International Back and Neck Pain Forum, Buxton, May 2016.

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Chapter One. Introduction

The research in this thesis is concerned with the epidemiological study of neuropathic pain in patients with low back-related leg pain (LBLP) consulting in primary care. In order to assist the reader in understanding the rationale for this focus, this first chapter outlines the current understanding of causal mechanisms underlying nociceptive and neuropathic pain. Methods of assessing and diagnosing neuropathic pain are briefly discussed and case ascertainment tools appropriate for use in both epidemiological research and primary care are presented and discussed. A section outlines the principles of epidemiology in primary care and the advantages of choosing primary care as a setting for prognostic research. The chapter summarises the literature on the frequency of neuropathic pain in the general population and heterogeneous populations of chronic pain. The penultimate section outlines the prevalence, characteristics and prognosis of neuropathic pain in low back pain (LBP) reported in the literature before the final section outlines the distinction between LBP and LBLP. A discussion is presented in the final section on the clinical diagnoses and underlying pain mechanisms related to LBLP.

1.1 Overview of pain

1.1.1 Definition of pain

The International Association for the Study of Pain (IASP) Task Force on Taxonomy, edited by Merskey and Bogduk (1994) define pain as:

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

The perception of pain is entirely subjective. Pain is always an unpleasant experience and is considered a psychological state (Merskey and Bogduk 1994).

1.1.2 Nociceptive pain

The term nociceptive pain is used to describe pain in a normally functioning somatosensory nervous system (Merskey and Bogduk 1994) where somatosensory refers to sensation (such as pain, pressure or warmth) which can occur anywhere within the body including the visceral organs, but not external to the body (for example, vision, hearing, olfaction). Not all activity in the nociceptors and in the nociceptor pathway result in pain, because a noxious stimuli has to be perceived psychologically to be painful. The following section will present an overview of some of the mechanisms of nociceptive pain that are important for the purpose of this thesis.

1.1.2.1. Mechanisms of nociceptive pain

After an injury, both thin (pain) and thick (touch, pressure and vibration) nerve fibres carry impulse signals from the site of injury to the dorsal horn of the spinal cord. At the dorsal horn, the impulse is transmitted through ascending tracts in the spinal column to the brain where the pain is perceived in the thalamus; this may trigger a descending signal to the area of injury which in turn may result in modulation of cell activity and the experience of pain. The perception of pain at any one time depends in part on the

previous experiences of the individual, the context in which they received the injury, and the current state of the individual's mood. Activity in both the thin and thick nerve fibres is important to consider because they have different roles in the transmission of pain signals. In a normal state, thin fibre activity tends to result in the transmission of signals to the brain whereas thick fibre activity tends to result in reduction of transmission, the more the thick (vibration, touch and pressure) fibre activity the less pain is perceived.

1.1.3 Neuropathic pain

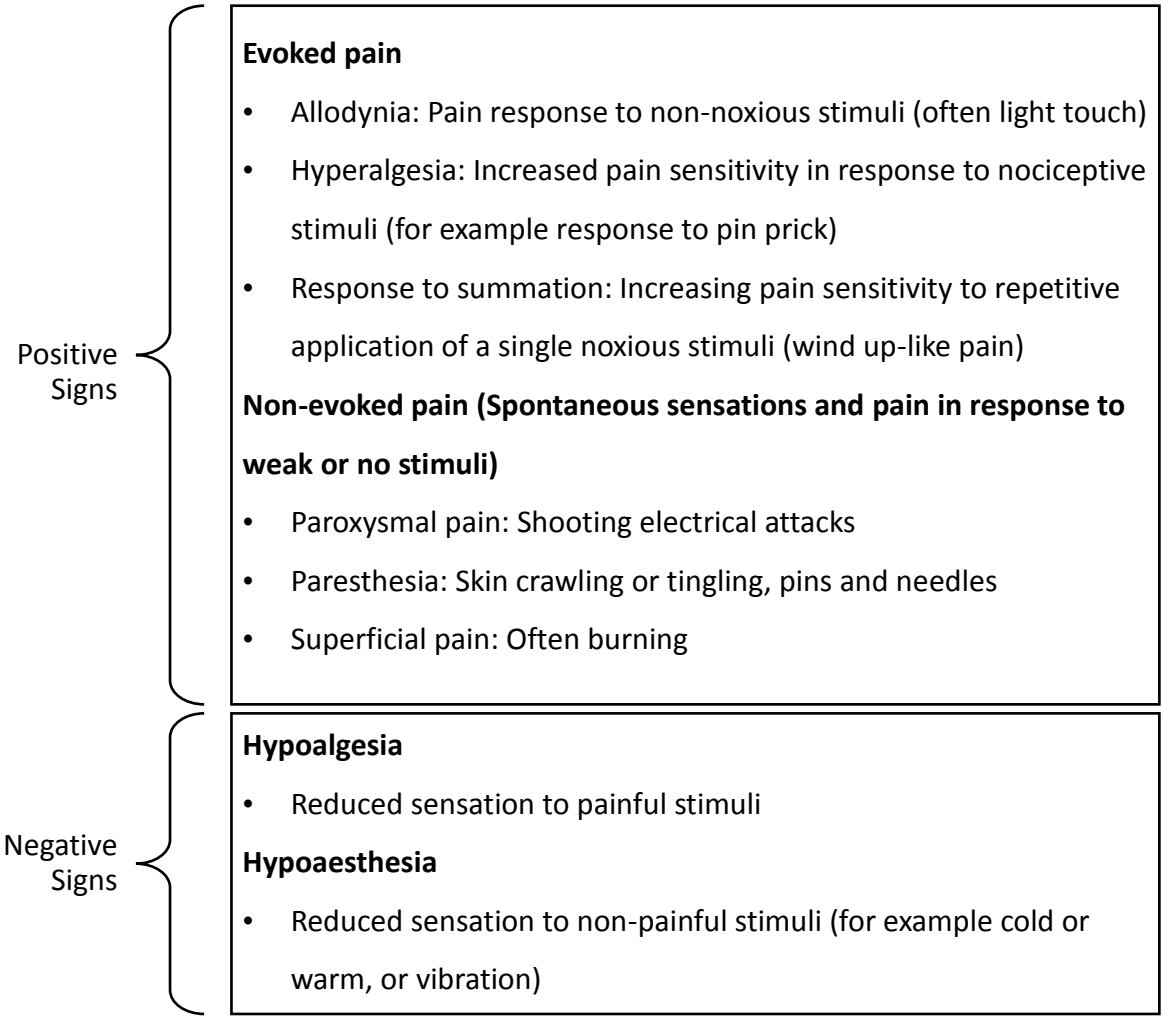
Nociceptive pain is considered to be an adaptive process which differs from neuropathic pain which is considered maladaptive. Neuropathic pain is defined by the Neuropathic Pain Special Interest Group of the International Association for the Study of Pain (IASP) (Treede et al. 2008) as:

> *Pain arising as a consequence of a lesion or disease of the somatosensory system.*

A lesion reflects abnormalities when there is trauma or injury (for example, spinal cord transection) and a disease is commonly used when the cause for the underlying lesion is known (for example, stroke, cancer or diabetes mellitus) (Merskey and Bogduk 1994). Neuropathic pain is a sub-group of neurogenic pain (Merskey and Bogduk 1994) and the implication of this is that neuropathic pain is irreversible. Patients with clinical conditions characterised by neuropathic pain may report symptoms such as electrical attack-like pain which are particularly distressing. Unlike in nociceptive pain,

neuropathic pain is characterised by spontaneous (non-evoked) pain such as electrical attacks or pins and needles (this is an example of a positive sign of neuropathic pain) and also a loss of function (also known as negative signs) (Baron et al. 2010). Figure 1.1 summarises the key features of both positive and negative signs. The pain system is not considered static and as such, the signs and symptoms of neuropathic pain may change during the course of the disease (Jensen and Baron 2003).

Figure 1.1 Key features of positive and negative signs of neuropathic pain



1.1.3.1 Mechanisms of neuropathic pain

In the event of an injury or lesion to the somatosensory system, a number of events occur both local to the site of injury and centrally in response to the injury. As with the mechanisms of nociceptive pain, an understanding of how mechanisms generate symptoms in neuropathic pain is important for the purpose of this thesis and an outline of mechanisms is provided in the discussion below. Further details can be found in a review on Neuropathic pain by Cohen and Mao (2014). At the site of a lesion, demyelination and cell death can lead to both positive and negative signs of neuropathic pain. Positive signs such as spontaneous pain are generated in part by abnormal impulse generation and electrical hyperexcitability (called ectopic excitability) at the site of injury (Devor 2013), and negative signs can result from loss of function because of a reduction in impulse conduction (Woolf 2004). Ectopic excitability in peripheral nerves contributes to neuropathic pain in two ways, firstly, it directly drives pain pathways in the central nervous system and secondly, it can trigger and maintain increased sensitivity of neurons in the central nervous system to normal or subthreshold peripheral nerve activity (also called central sensitisation) (Devor 2013).

Central sensitisation is not exclusive to neuropathic pain; in both neuropathic and nociceptive pain conditions, changes in the spinal cord and in the higher centres of the brain are in part, characterised by an amplification of pain. Amplification arises when thick nerve fibres that normally do not produce pain undergo a change in cellular characteristics that results in normally non-noxious stimuli being perceived as noxious

(described as allodynia) (Devor 2013). This process by which the nerve changes its function is synonymous with alterations in gene expression and is described as a phenotypic switch. The phenotypic switch in this case brings about a change in cellular characteristics that increases the expression of inflammatory mediators (Cohen and Mao 2014). The following section (1.1.4) outlines the role of inflammatory mediators in both neuropathic and nociceptive pain mechanisms, and then section 1.1.5 outlines how sensitisation at the level of the spinal cord contributes to the phenomena of referred pain.

1.1.4 Pain from mixed mechanisms

The mechanisms underlying nociceptive and neuropathic pain involve inflammatory pain responses (Devor 2013). The role of inflammation in nociceptive pain is considered to be a necessary part of the healing process in the acute stages, and these mechanisms are well established (Bennett 2006). In neuropathic pain conditions, where nerve damage causes inflammation and also inflammation causes ongoing nerve damage, the underlying process is less clear (Bennett 2006). Conceptually and in terms of clinical application it is difficult to make a clear distinction between neuropathic and inflammatory pain (Bennett 2006). In fact, inflammatory pain, neuropathic pain and nociceptive pain often co-exist. A space occupying tumour can simultaneously apply noxious force on adjacent healthy tissue (nociceptive pain), directly injure nerves (neuropathic pain) and trigger an inflammatory response (Devor 2013). The presence of one type of pain does not infer the absence of the other type of pain and the three clinically co-exist together.

1.1.5 Pain referral

Referred pain is that perceived in a region topographically distinct from the region in which the actual pain source is located, is thought to be caused by amplification of neurons in the spinal cord and is assumed to be non-neuropathic in nature (Merskey and Bogduk 1994). Referred pain can occur in both somatic tissue and visceral tissue, a common example in somatic tissue is the self-report of buttock or leg pain arising from degenerative changes in the facet joints. In this example, pain referred to the buttock or leg may be caused by convergent inputs to spinal cord neurons receiving inputs from sensory neurons of the facet joints as well as the remote tissues of the leg or buttock (Treede et al. 1992). In the example given of facet joint degeneration, the location of the remote pain in the leg is associated with the intensity and duration of the activation of the sensory inputs from the facet joint.

The classical view of the natural history of patients with nociceptive pain is that of a favourable prognosis whereas that of patients with neuropathic pain appears different, with many people with neuropathic pain often living with persisting pain (Ciaramitaro et al. 2010). This chapter now proceeds to discuss some of the key concepts of prognosis research in pain, and then the relevance of settings in pain research (Section 1.2). This is before section 1.3 which provides an outline of the methods commonly used to assess neuropathic pain in clinical practice and in epidemiological research, and an outline of how neuropathic pain is currently managed in clinical practice before presenting the epidemiology of neuropathic pain in common clinical conditions.

1.2 Prognosis of pain in primary care

The term “prognosis” refers to the risk of future health outcomes in people with a particular disease or health condition, in the context of this thesis the health condition is neuropathic pain. The prognosis of patients with neuropathic pain is thought to be worse than those with nociceptive pain. Overall prognosis research answers questions such as, “what is the most likely course of this patient with this health condition”. In patients who consult with health care professionals, overall prognosis describes the clinical course rather than natural history of a condition as it takes into consideration that a patient would have undergone some form of diagnostic assessment with a treatment plan. To improve the likely clinical course of patients with neuropathic pain, evidence is required on whether specific characteristics (prognostic factors) are associated with future endpoints such as neuropathic pain-related disability or persistence of pain (Hemingway et al. 2013). Information comes from prospective observational studies where the temporal relation between a prognostic factor and given endpoint can be investigated. A prognostic factor is defined as a biological, behavioural, symptomatic, psychological or environmental measure that can be modifiable (for example body mass index) or non-modifiable (for example family history) and is associated with a future outcome (Riley et al. 2013). Prognosis research informs clinicians and patients on an individual level and provides valuable information for public health policy (Hemingway et al. 2013).

1.2.1 Primary care as a setting for research

The setting in which pain is studied is crucial to the questions posed and the interpretation of prognosis research findings. The first point of contact for an individual with pain entering the health care system in the UK is usually a primary care provider (Costa Lda et al. 2013) such as a general practitioner, or other clinicians such as practice nurses, physiotherapists or osteopaths. The majority of patients with pain are managed in primary care rather than in specialist pain centres (Breivik et al. 2006). In the current literature on pain, specialist pain services have been used extensively to provide access to large numbers of patients for research. It is likely that populations of patients drawn from specialist pain services are systematically different than patients consulting in primary care which limits the generalisability of research findings (Crombie and Davies 1998). Epidemiological studies that draw from primary care rather than specialist pain settings have key advantages. One advantage is that estimates of prevalence and characteristics of a condition of interest are likely to more accurately reflect the problem in the general population than studies in set in specialist pain centres (Tager 1998). The epidemiology of neuropathic pain in primary care is important for many reasons. It provides valuable information on the prevalence, characteristics in terms of symptom duration, and severity of neuropathic pain within a condition. Such evidence may be very useful in developing better management strategies in those patients with neuropathic pain.

1.3 Neuropathic pain

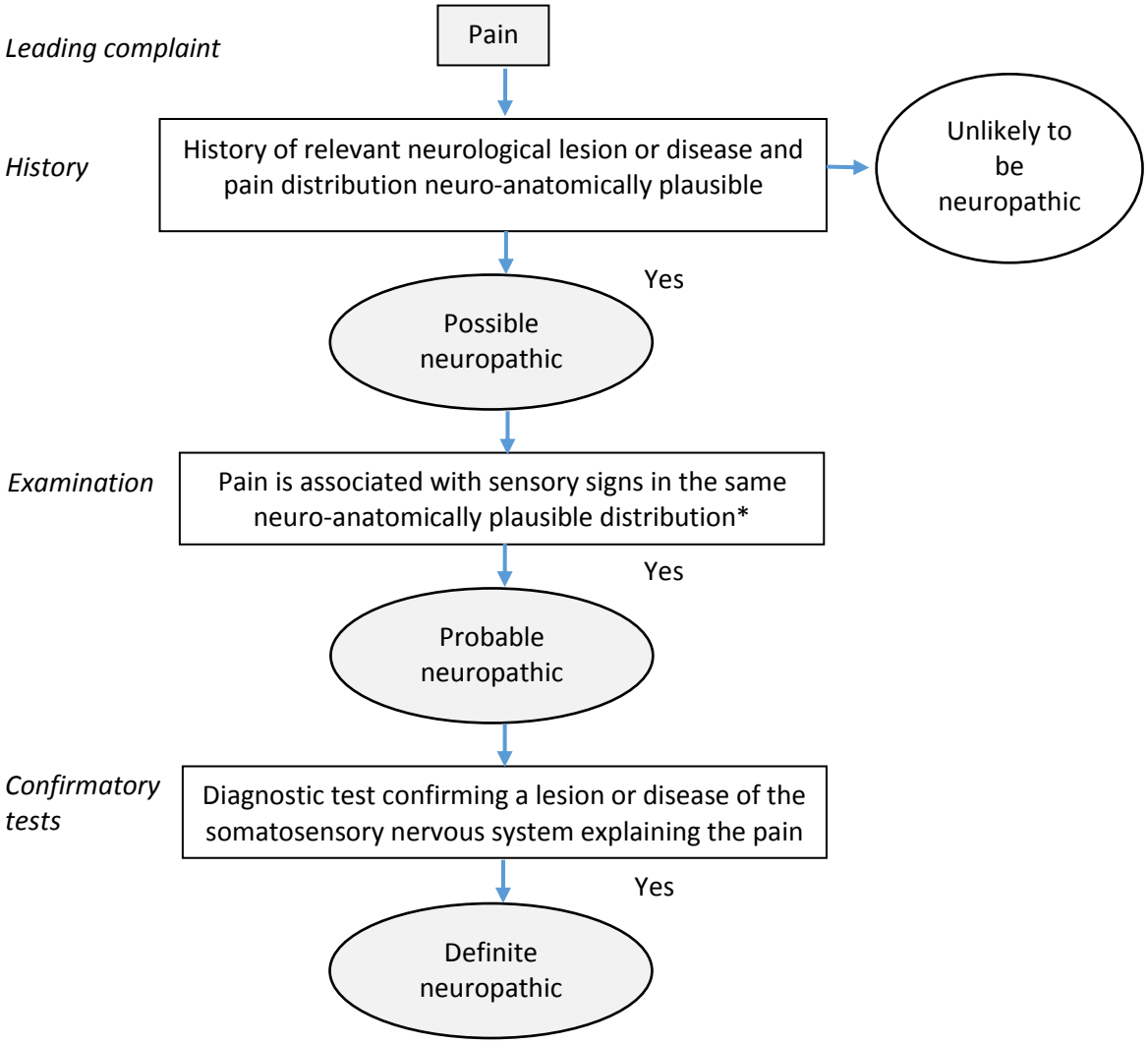
1.3.1 Assessment of neuropathic pain

Neuropathic pain is a clinical description (and not a diagnosis) (Merskey and Bogduk 1994). Detecting neuropathic pain can present with difficulties. There is not one sign or symptom that is exclusively attributed to neuropathic pain, nor is there absolute consensus on how patients with neuropathic pain should be identified in clinical practice or epidemiological research. This section discusses how, in the absence of a gold standard, patients with neuropathic pain are commonly identified in both clinical practice and for the purposes of epidemiological research. A number of neuropathic pain case ascertainment tools that are commonly cited in the neuropathic pain literature are described in section 1.3.1.2 and are summarised in Tables 1.2 and 1.3.

1.3.1.1 Assessment using clinical examination

There is some consensus that in clinical practice, patients with neuropathic pain are identified by clinical history and examination (Treede et al. 2008). The Neuropathic Pain Special Interest Group of IASP proposed a hierarchical classification system with four criteria based on clinical examination and confirmatory tests (Treede et al. (2008) updated by Finnerup et al. (2016)). Figure 1.2 reproduces the updated grading system reported by Finnerup et al. (2016).

Figure 1.2 Updated hierarchical classification system for patients with neuropathic pain. Reproduced with permission from Walters Kluwer Health (Finnerup et al. 2016)



*The area of sensory changes may extend beyond the innervation territory. Neurological examination may include sensory examination of touch, vibration, pin-prick, cold and/or warm. Sensory loss is generally required to be present for patients to meet criterion of "probable" neuropathic pain.

In specialist pain settings, clinical history and an extensive neurological examination may identify patients at best as having "probable" neuropathic pain, additional confirmatory tests may identify patients with "definite" neuropathic pain but despite investigations the cause of the pain often remains unknown (Cruccu and Truini 2009).

In primary care where clinicians are non-specialists, patients would be identified at best as having “possible” neuropathic pain. It is questionable whether forms of assessment that are offered in specialist pain settings are clinically useful in settings such as primary care where the majority of patients with neuropathic pain are managed (Breivik et al. 2006). In epidemiological research too, a more detailed assessment other than clinical examination is generally unattainable (Smith and Torrance 2010). Questionnaires or case ascertainment tools potentially provide benefit to the clinician by facilitating early diagnosis and decision-making about appropriate treatment. Academically, questionnaires allow for population-based epidemiological studies and clinical trials (Smith and Torrance 2010). Simple tools have been developed for use in research and in clinical practice where complex and time consuming methods of assessment are not possible.

1.3.1.2 Assessment using neuropathic pain case ascertainment tools

This section provides a description of neuropathic pain case ascertainment tools commonly cited in the published literature. Case ascertainment tools for the purposes of epidemiological study in neuropathic pain need to detect features of pain that are characteristically neuropathic in an efficient, valid and reliable manner (Smith and Torrance 2010). One of the first tools to use sensory descriptors of neuropathic pain was the McGill Pain Questionnaire (Boureau et al. 1992). It identifies six sensory descriptors that are more commonly used by patients with neuropathic pain, these were: “electric shock”, “burning”, “cold”, “pricking”, “tingling” and “itching”. These six

descriptive words have been used in a number of subsequent tools that attempt to screen and identify cases of neuropathic pain.

These tools include: the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) (Bennett 2001), the Douleur Neuropathique en 4 questions (DN4) (Bouhassira et al. 2005), painDETECT (Freynhagen et al., 2006), Neuropathic Pain Questionnaire (Krause and Backonja 2003) and ID Pain (Portenoy 2006). All have been adapted for use in a number of languages, neuropathic pain disorders (i.e. diabetic neuropathy, radicular pain/sciatica, and trigeminal neuropathy) and health care settings and at best describe patients with "possible" neuropathic pain (Smith et al. 2012a). The LANSS, PainDETECT and DN4 have been used in populations relevant to low back pain (for example, Walsh et al. (2012) and Beith et al. (2011)). LANSS was subsequently developed into a self-report version, the s-LANSS (Bennett et al. 2005). Each of these tools are presented in more detail below, the methodology used in the development of each tool is considered in Table 1.1, and the reported sensory and physical items and scoring is reported and compared in Table 1.2.

1.3.1.2.1 LANSS and s-LANSS

LANSS (Bennett, 2001) was developed in two populations with chronic pain, and consists of a seven-item pain scale including five sensory descriptors and two items of clinical examination with a simple, weighted scoring system. Clinical diagnosis was classified by one clinician based on clinical features, known pathology, and radiological or electro-physical evidence. The tool was then validated in a second group of patients with nociceptive and neuropathic pain (known pathology of mixed origin) (n=40)

(Bennett, 2001). A score of 12 or more (out of a possible 24) suggests neuropathic pain. Further research has led to the development of a self-report, self-examination of the LANSS (Bennett et al., 2005), known as s-LANSS. Individual items of s-LANSS reported the following changes: dysesthesia, autonomic (for example, red mottled changes to the skin), evoked, paroxysmal, thermal, allodynia and tenderness or numbness. S-LANSS has also been used in back pain populations within the UK (Walsh et al. 2012).

1.3.1.2.2 DN4

The DN4 was originally developed in France (Bouhassira et al., 2005) where a small number of items was found to be able to discriminate neuropathic pain. It consists of four questions sub-divided into seven items related to the history taken from the patient and three items taken from the physical examination. It was initially tested in 160 pain clinic patients and has been tested in a variety of chronic pain conditions including LBP (Attal et al. 2011). It has been translated into different languages using different pain populations, including LBLP (Walsh et al., 2012).

1.3.1.2.3 PainDETECT

PainDETECT (Freynhagen et al., 2006) was developed in a population of patients with LBP in Germany. It includes seven weighted sensory descriptor items and two items relating to the radiating and temporal characteristics of the pain pattern and is completed by self-report. Patients are classified by painDETECT scores as having “likely nociceptive pain”, “unclear pain” mechanism and “possible neuropathic” pain. The questionnaire has been used in LBLP populations (Beith et al. 2011) and validated

further in fibromyalgia (Gauffin et al. 2013) and neck and upper limb pain (Tampin et al. 2013).

Table 1.1 Comparison of methodology used in neuropathic pain case ascertainment tools

Tool	Format	Methods	Reference Standard	Sensitivity (%)*	Specificity (%)*
LANSS	5 pain descriptors +2 physical tests	Study 1: 30 neuropathic (mixed chronic pain) versus 30 nociceptive pain patients. Study 2: 20 neuropathic versus 20 nociceptive pain patients	Clinical diagnosis taking into account clinical features, known pathology, radiological evidence and electrophysiological evidence if available.	83	87
s-LANSS	7 self-report questions	Study 1: Clinic study of 100 patients with neuropathic pain versus 100 patients with nociceptive pain. Study 2: Postal study of 310 patients	Clinical diagnosis on the basis of history, clinical examination and investigations.	74 (completion by self-report) 74 (completion by interview)	76 (completion by self-report) 83 (completion by interview)

Tool	Format	Methods	Reference Standard	Sensitivity (%)*	Specificity (%)*
DN4	7 pain descriptors +3 physical tests	Study of 89 patients with pain due to a nerve lesion and 71 patients with a non-neurological lesion	Clinical diagnosis by medical history, physical examination, electromyography and imaging when indicated.	80	92
Pain-DETECT	9 self-report questions	Study 1. Validation study of 228 neuropathic and 164 nociceptive patients. Study 2: Epidemiological survey of 7,772 low back pain patients	Clinical diagnosis with appropriate diagnostic methods including neurological and electrophysiological imaging.	85	80

Abbreviations: DN4, Douleur Neuropathique en 4 questions. LANSS, Leeds Assessment of Neuropathic Symptoms and Signs. S-LANSS, Self-report version of the Leeds Assessment of Neuropathic Symptoms and Signs. *Derived from development study

Table 1.2 Comparison of sensory descriptors, physical tests and scoring in neuropathic pain case ascertainment tools

Item			**LANSS**	**s-LANSS**	**DN4**	**PainDETECT**
Patient interview						
Pain course pattern						-1 to 1
Pain radiation						0 or 2
Pain descriptor /quality	*Non-painful sensations*	*Pricking or tingling, like pins and needles*	0 or 5	0 or 5	0 or 1*	0-5§
		Itching			0 or 1	
		Numbness			0 or 1	0-5 §
	Pain quality	*Electric shock or shooting*	0 or 2	0 or 2	0 or 1	0-5 §
		Burning	0 or 1	0 or 1	0 or 1	0-5 §
	Evoked pain	*Mild/blunt pressure*				0-5 §
		Warm or cold				0-5 §
		Light touching	0 or 3	0 or 3		0-5 §
	Brush			0 or 5		

Item		LANSS	s-LANSS	DN4	PainDETECT
Altered threshold	*Pin-prick*		0 or 3 ‡		
Changes in skin		0 or 5	0 or 5		
Clinical examination					
	Light touching			0 or 1†	
	Brush	0 or 5 ‡		0 or 1‡	
	Pin-prick	0 or 3 ‡		0 or 1†	
Scoring					
Score range		0 to 24	0 to 24	0 to 10	-1 to 38
Score interpretation		≥ 12 neuropathic < 12 non-neuropathic	≥ 12 neuropathic < 12 non-neuropathic	≥4 neuropathic, < 4 non-neuropathic	≥ 19 likely neuropathic, 13-18uncertain neuropathic. ≤12 unlikely neuropathic

Abbreviations: DN4, Douleur Neuropathique en 4 questions. LANSS, Leeds Assessment of Neuropathic Symptoms and Signs. S-LANSS, Self-report version of the Leeds Assessment of Neuropathic Symptoms and Signs. *Score of 1 given for tingling *and* score of 1 given to pins and needles. † Score given for decreased response. ‡ Score given for stimulus evoked pain. § For each question: never, 0; hardly noticed, 1; slightly, 2; moderately, 3; strongly, 4; very strongly, 5.

Use of each of the four tools reported in this section (1.3) is likely to result in some failure to identify patients with clinically diagnosed neuropathic pain, and it is possible they may also over-identify patients because the tools are too broad and imprecise (Smith and Torrance 2010). However, case ascertainment tools are easy to use by professionals and by patients alike, in clinic or via telephone or by mail and without a gold standard with which to compare an assessment tool for neuropathic pain, the questionnaires provide interesting interim estimates (Smith and Torrance 2010). PainDETECT, DN4 and s-LANSS have been used in cross-sectional epidemiological surveys in mixed populations of neuropathic pain, to report prevalence. (Bouhassira et al. 2008, Torrance et al. 2006, Nakamura et al. 2014).

1.3.2 Management of neuropathic pain

There are specific medications available in both primary care and specialist pain settings for patients with neuropathic pain conditions. Guidelines advocate the use of specific neuropathic pain medication, such as Duloxetine, Amitriptyline, Pregabalin and, or Gabapentin and in some instances Tramadol (NICE CG173 2013, Finnerup et al. 2015), and non-pharmacological treatments such as physiotherapy or cognitive behavioural therapy (NICE CG173 2013). In primary care, of patients with chronic pain conditions and neuropathic pain, just less than half are treated with an adequate trial of a neuropathic drug and over half do not receive any targeted pharmacological treatment for neuropathic pain (Torrance et al. 2013). Of those patients treated with specific neuropathic medications a small proportion do not respond and are considered to have “refractory” neuropathic pain (Torrance et al. 2013). Failure to

treat patients with neuropathic pain using specific medication may be in part because these patients go undetected, especially in primary care (Torrance et al. 2013) and in part due to a differences in the response to both pharmacological and non-pharmacological treatment (Baron et al. 2012, Martin et al. 2014). Despite current guidelines advocating the use of specific neuropathic pain medications, the condition itself is difficult for clinicians and in turn patients to manage. Prognosis research is likely to inform clinicians of the likely course of neuropathic pain, to assist clinicians to identify patients who will or will not have a favourable outcome and to use this information to better inform clinical decision-making about treatment.

1.3.3 Epidemiology of neuropathic pain

1.3.3.1 Frequency of neuropathic pain

Current estimates of the frequency of neuropathic pain in primary care are derived from estimates in the general population (van Hecke et al. 2014) or from specialist pain settings. The prevalence of neuropathic pain in the general population, derived in part using neuropathic case ascertainment, was estimated to be between 6.9% and 10% (van Hecke et al. 2014). The frequency of neuropathic pain varies from condition to condition but for three commonly cited neuropathic conditions (post-herpetic neuralgia, trigeminal neuralgia and painful diabetic neuropathy) the incidence was less than one 1/1,000 person years for each condition (van Hecke et al. 2014). Prevalence estimates of neuropathic pain in patients with chronic pain, including chronic widespread pain and soft tissue syndromes (for example, tendinopathy, fibromyalgia and musculoskeletal pain) varied from 13% to 43.3% (Fishbain et al 2014). LBP is

among the most common presentations of neuropathic pain in UK primary care (46.4%) (Berger et al. 2012, Torrance et al. 2014). The variation in the estimates provided here highlights the importance of establishing best estimates within one neuropathic pain condition, but given the challenge in agreeing a case definition, an understanding of the key characteristics and prognosis of these patients with neuropathic pain may be more appropriate.

1.3.3.2 Characteristics of neuropathic pain

Previous research reports that individuals with chronic pain thought to be neuropathic may be more likely to be female, no longer married, with no educational qualifications and to be smokers (Torrance et al. 2013, Torrance et al. 2014) than those with chronic pain that was thought to be non-neuropathic. Those with chronic pain thought to be neuropathic in nature may be more likely to be living in council rented accommodation than those without (Torrance et al. 2013, Torrance et al. 2014); housing status was reported to be a proxy for social class (Stoate 1989). The incidence of neuropathic pain may increase with increasing age (Hall et al. 2013). In individuals with neuropathic pain, three-quarters report moderate to severe pain (Bouhassira et al. 2008) and increased pain severity was associated with increased disability and higher medication use compared to those with chronic pain without neuropathic features (Schaefer et al. 2014). Most individuals with neuropathic pain reported pain in two or more locations (Bouhassira et al. 2008) and one quarter suffered with other health problems, in particular anxiety and depression (de Andres et al. 2014, Bouhassira et al. 2008). In the general population, 24% of individuals with neuropathic pain considered themselves

disabled (Schaefer et al. 2014) and individuals with neuropathic pain related to chronic pain were more likely to be unable to work than those without neuropathic pain (Torrance et al. 2006).

1.3.3.3 Prognosis of neuropathic pain

There is an assumption that neuropathic pain is irreversible (Merskey and Bogduk 1994) but in clinical practice as an episode of pain improves the signs and symptoms of neuropathic pain often recede accordingly. The notion that the course of neuropathic pain can vary in individuals is supported by the literature (Baron et al. 2016) but empirical evidence from prospective cohort studies is scarce. There is some evidence from one systematic review for a number of potential prognostic factors associated with persistent neuropathic pain including male gender, older age, smoking, lower health status and higher pain severity (Boogaard et al. 2015). However, there was little consistency of the definition of persistent neuropathic pain itself and little consistency across different neuropathic pain definitions. In a Delphi consensus study of experts in neuropathic pain, Boogaard et al. (2011) reported that psychological characteristics were perceived to be the strongest prognostic factors associated with persistent neuropathic pain, this was perhaps a surprising finding since the first line treatment for neuropathic pain is generally considered to be pharmacological (NICE NG59 2016, NICE CG173 2013). Overall, the presentation of patients with neuropathic pain appeared worse in terms of pain severity and disability compared to patients without neuropathic pain. It is evident that there is a substantial variation in prevalence,

characteristics and prognostic factors across neuropathic pain conditions, across settings and definitions of neuropathic pain.

1.4 Low back pain

1.4.1 Overview

LBP is the leading cause of disability globally (Buchbinder et al. 2013) and with an aging population this level of burden is likely to continue, LBP is therefore a major public health problem. Most people will experience an episode on LBP at some point in their lives (Hoy et al. 2012a). LBP is defined as pain typically between the lower rib margins and the buttock creases (Dionne et al. 2008) and can present with pain in one or both legs (Hartvigsen et al. 2018, Chou 2010). In LBP, nociceptive pain arises from activation of nociceptors of the innervated part of the intervertebral disc, ligaments, joints, fascia, and muscles of the spinal segment as a response to injury, biomechanical stress or inflammation. In the majority of cases, the source of pain cannot be identified and those patients are classified as having non-specific LBP (Maher et al. 2017). In some cases, patients with LBP present with leg pain and neurological symptoms in the legs as a result of injury to the spinal nerve root, the most common cause of injury is a disc herniation (Porchet et al. 2002). Pain arising from damage or compression to the nerve root is considered to be neuropathic (Baron et al. 2016).

1.4.2 Epidemiology of neuropathic pain in LBP patients

The following sections describes the epidemiology, in terms of prevalence characteristics and prognosis of neuropathic pain in LBP patients and Table 1.3

summarises studies that report prevalence, characteristics and prognosis of neuropathic pain in this patient population.

1.4.2.1 Prevalence of neuropathic pain in LBP patients

The prevalence of neuropathic pain in LBP at any one point in time and in any setting has been estimated to range from 2% in a sample of older patients with acute LBP (Enthoven et al. 2013) to 90%, in a study with a group of workers who regularly consulted with chronic LBP (Mehra et al. 2012). Variation in prevalence may not be only due to clinical setting but also due to patient selection. Low prevalence of neuropathic pain was reported in axial back pain symptoms (12%, Forster et al., 2013) and in LBP without evidence of sensory loss or severe motor deficits on neurological examination (15%, Hiyama et al. (2015)), whereas higher prevalence was reported in LBP populations with and without leg pain (average of 50% across studies; (El Sissi et al. 2010, Kaki et al. 2005, Hassan et al. 2004)). In the same patient population, Sakai et al (2015) used both PainDETECT and the Japanese neuropathic screening questionnaire (Matsubayashi et al. 2013) to estimate neuropathic pain prevalence, and reported it to be 16% and 44%, respectively. The difference in case ascertainment tools to derive neuropathic pain appear to generate significantly different prevalence estimates of neuropathic pain. Prevalence of neuropathic pain in samples derived from the general population was lower than that of settings that included specialist pain centres (19% versus 36% (Schmidt et al. 2009)).

Table 1.3 Characteristics of studies showing prevalence of neuropathic pain in low back pain, grouped by setting in primary care or mixed setting (primary and, or secondary and, or tertiary care)

Study	Study design includes longitudinal data?	Sample*	Method for identifying neuropathic pain	Setting	Prevalence of neuropathic pain (%)
Cappelleri et al. (2017)	No	Diagnosis of CLBP associated with NeuP: n=103, (NR)%M, Age (NR)	PainDETECT	33 Community based physician practices in United States (includes general practitioners, neurologists, pain specialists and endocrinologists)	63
Enthoven et al. (2013)	No	LBP[†] patients aged >55 years: n=250, 40 %M, Age: 66 (8)	DN4 plus physical examination	GP consulters in Netherlands	2

Study	Study design includes longitudinal data?	Sample*	Method for identifying neuropathic pain	Setting	Prevalence of neuropathic pain (%)
El Sissi et al. (2010) ††	No	LBP: n= 1134, 60%M, Age: 45 (12)	LANSS	Outpatient medical setting (includes medical surgical, orthopaedics, general practitioners, neurologists and pain specialists)	55
Forster et al. (2013) ††	No	Axial§ LBP: n= 1083, 42%M, Age: 58 (15)	PainDETECT	450 outpatient centres in Germany (GPs, rheumatologists, orthopaedics and pain specialists)	12
Freynhagen et al. (2006b)††	No	CLBP: n=7772, (NR)%M, Age: 57 (NR)	PainDETECT	158 GPs, 45 orthopaedics, 67 neurologists, 202 pain clinics	37

Study	Study design includes longitudinal data?	Sample*	Method for identifying neuropathic pain	Setting	Prevalence of neuropathic pain (%)
Hassan et al. (2004) [††]	No	CLBP: n=100, 69%M, Age: NocP 42 (11), NeuP 50 (13)	LANSS	10 "centres" across the middle east region	41
Hiyama et al. (2015)	No	LBP[||]: n=331, 58%M, Age NocP 54 (17), NeuP 57 (15)	Japanese version of PainDETECT	Japanese suburban tertiary care centre	15
Kaki et al. (2005) [††]	No	CLBP: n= 1125, 60%M, Age 47 (13)	LANSS	Mixed outpatient setting: neurologist, neurosurgeons, pain specialists, rheumatologists, orthopaedic	55

Study	Study design includes longitudinal data?	Sample*	Method for identifying neuropathic pain	Setting	Prevalence of neuropathic pain (%)
Kew et al. (2017)	No	LBP ≥ 1 month: n=210, 39%M, Age: 58 (NR)	PainDETECT	Tertiary referral spine clinic in Malaysia	12
Mehra et al. (2012) ‡‡	No	LBP: n=39425, 36%M, Age: 51 (NR)	ICD-9 codes for neuropathic pain	US patient commercial insurance claims integrated database**	90
Sakai et al. (2015)	Yes, follow-up data	CLBP‡: n=30, 70%M, Age: 72 (6)	PainDETECT and Neuropathic screening questionnaire (Japanese)	National Centre for Geriatrics and Gerontology	PainDETECT: 16 Neuropathic screening questionnaire: 44

Study	Study design includes longitudinal data?	Sample*	Method for identifying neuropathic pain	Setting	Prevalence of neuropathic pain (%)
Schmidt et al. (2009) ††	No	LBP (Sample 1): n=6920, 38%M, Age: 51 (12)	PainDETECT	500 general practices and specialist pain practices and in hospitals across Germany.	36
	No	LBP (Sample 2): n=1718, 44%M, Age: 50 (14)	PainDETECT	German back pain research network study: population survey **	19

Abbreviations: CLBP, chronic low back pain. DN4, doleur Neuropathique-4. ICD-9, International Classification of Diseases, 9th-Revision. LANSS, Leeds assessment of neuropathic symptoms and signs neuropathic pain scale. LBP, low back pain. M, male. NR, not reported. NocP, nociceptive pain. NeuP, neuropathic pain.

* Age written as mean (standard deviation) years

† Back pain includes whole region of spine from top of shoulder blades to first sacral vertebra

‡ Chronic LBP (back pain > leg pain), whose condition was ineffective on NSAID

Patients were excluded if they presented with pain radiating into the leg or other body sites§, or findings of sensory loss of severe motor deficits on neurological examination||

** Samples based on surveys rather than clinical settings

†† Supported by Pfizer

‡‡ Supported by Johnson & Johnson

1.4.2.2 Characteristics and prognosis of neuropathic pain in LBP patients

Neuropathic LBP was not associated with either female or male sex (El Sissi et al. 2010, Enthoven et al. 2013, Freynhagen et al. 2006b, Hassan et al. 2004, Kaki et al. 2005, Kew et al. 2017). There was evidence of inconsistent findings about age in LBP patients with neuropathic pain. Three studies reported no difference in age between patients with and without neuropathic pain (Enthoven et al. 2013, Freynhagen et al. 2006b, Kew et al. 2017) whereas older age was associated with neuropathic pain in two studies (Kaki et al. 2005, Hassan et al. 2004). Smoking was not strongly associated with neuropathic pain in LBP (Hassan et al. 2004, Kaki et al. 2005, El Sissi et al. 2010).

Patients with neuropathic LBP were more likely to report more severe pain (Freynhagen et al. 2006a, Kew et al. 2017), higher disability, higher levels of anxiety and depression (Freynhagen et al. 2006a, Schmidt et al. 2009, Kew et al. 2017) compared to those without. There was conflicting evidence that patients with neuropathic LBP present with more co-morbidities compared to those without (El Sissi et al. 2010, Hassan et al. 2004, Kew et al. 2017). Disc prolapse and spinal stenosis were associated with more features characteristic of neuropathic pain than nociceptive pain (Kaki et al. 2005, El Sissi et al. 2010), and degenerative disc disease was unlikely to be associated with neuropathic pain features in LBP (El Sissi et al. 2010). Neuropathic pain was associated with the presence of leg pain (Kew et al. 2017) in LBP patients compared to those without, and commonly, patients with neuropathic pain had below the knee pain (Enthoven et al. 2013, Kew et al. 2017).

One study of 30, elderly LBP patients with and without neuropathic pain (Sakai et al. 2015) reported on the effectiveness of the neuropathic pain medication Pregabalin over a four week period. In this study, both patients with and without neuropathic pain improved over time in terms of back pain intensity. However, overall there was no evidence of prognostic factors research in LBP patients with neuropathic pain.

1.5 Low back-related leg pain

Section 1.4 highlights the low prevalence of neuropathic pain in patients with LBP alone and shows that LBP patients with neuropathic pain present with more severe pain and higher LBP-related disability, compared to those without. Neuropathic pain was reported to be associated with pain location and patients with neuropathic pain commonly presented with LBLP. Compared to LBLP, LBP without leg pain is most likely assumed to be nociceptive whereas LBLP may be neuropathic, and some patients present with neurological signs and symptoms in the legs (Hartvigsen et al. 2018).

About two thirds of patients with LBP, in both primary and secondary care settings, present with leg pain (Hill et al. 2011a, Kongsted et al. 2012). Patients with LBLP suffer with higher pain, disability and poorer quality of life compared to those patients with LBP alone (Konstantinou et al. 2013). LBLP is considered an obstacle to recovery (Burton et al. 1995, Cherkin et al. 1996, Shaw et al. 2001) or a marker of severity (Hill et al. 2011a), the further the pain radiates down the leg, the greater the likelihood of increased disability and health care use (Selim et al. 1998, BenDebba et al. 2000, Hicks et al. 2008).

LBLP can be clinically diagnosed as either referred or radicular in nature, where radicular pain is understood to be caused by compression or irritation of a lumbar spinal nerve root for any reason, and referred leg pain may be due to pain from any other lumbar spinal tissue than the nerve root (Bogduk 2009) (the reader is referred to section 1.1.5 (page 7) for a report and an example of referred pain). Radicular pain refers to the symptom of pain that arises from one or more of the nerve roots. The terms “radicular pain” and “nerve root pain”, are not synonymous with “radiculopathy”. It is common for patients with radiculopathy to have radicular pain, but the term “radiculopathy” refers to a complex of symptoms of neurological deficit, pain and sensory characteristics that are concurrent with neuropathic pain (Wolff and Levine 2002). In LBLP, sciatica is the most common term used in the literature to denote lumbar radicular pain with or without evidence of radiculopathy (Konstantinou and Dunn 2008). Recent guidelines use the term sciatica for describing radicular pain (NICE NG59 2016) and for consistency the term sciatica will be used throughout this thesis.

The mechanisms underlying sciatica are assumed to be neuropathic as the pain is arising from involvement of a nerve root, whereas the mechanisms underlying referred leg pain are assumed to be nociceptive in nature (Merskey and Bogduk 1994). Sciatica is classically described in textbooks as a narrow band of lancinating pain travelling down the back of the lower limb (Bogduk 2009) and referred leg pain as dull, aching pain in an ill-defined distribution (Cohen and Mao 2014) but without any features of neural involvement. Classification by dichotomising LBLP into either referred leg pain

or sciatica may provide simplicity but the clinical reality is that patients rarely present with clear presentation of either sciatica or referred leg pain (Murphy et al. 2009). It is likely that there is considerable overlap between both clinical features and mechanisms underpinning sciatica and referred leg pain.

1.6 Summary

This chapter has presented an overview of current knowledge about nociceptive and neuropathic pain mechanisms, including a discussion of the role of sensitisation and referred pain. The chapter highlights the complexity of identifying cases of neuropathic pain in clinical practice and in epidemiological research. An outline is provided on the role of prognosis research and the use of primary care as a setting in this thesis. Furthermore, this chapter has presented the epidemiology of neuropathic pain in its broadest context and more specifically in patients with LBP. As discussed in this chapter, previous research has shown that LBP patients with neuropathic pain present with more severe pain and LBP-related disability compared to those without but evidence on prognosis was limited. This chapter presented the distinct differences in the underlying pain mechanisms between LBP and LBLP. The following chapter presents the rationale, aims, objectives and outline of the research in this thesis.

Chapter Two. Rationale, aims and objectives

This chapter provides the rationale, the aims and objectives of the research in this thesis and concludes with an outline of the contents of the subsequent chapters in this thesis.

2.1 Thesis rationale

The previous chapter highlighted that patients with neuropathic LBP seem to present with higher levels of pain severity and pain related disability than those LBP patients without. The chapter also highlighted inconsistencies in the literature and a large variation in prevalence estimates, in part this may be because the LBP population is broadly defined and heterogeneous in nature. This thesis focuses on a subgroup of LBP, those patients with LBLP because it is leg pain that is thought to be caused by neuropathic pain mechanisms, whereas the mechanisms underlying LBP alone (also called axial back pain) are more likely to be nociceptive. LBLP is common and is associated with increased pain, disability and poorer quality of life compared to LBP alone and for this reason there is an argument that LBLP patients should be considered as distinct for research purposes (Coggon et al. 2016). Not all LBLP is thought to be neuropathic, LBLP is clinically diagnosed as having sciatica or referred leg pain, where sciatica is thought to be neuropathic and referred leg pain to be nociceptive. There is evidence that in clinical practice, the mechanisms underlying LBLP are not clearly delineated, it is not clear what proportion of LBLP patients do have neuropathic pain and although it is not known with certainty, it is widely thought that these patients with neuropathic pain do worse over time compared to those without. Understanding

the pain mechanisms underlying back pain presentations such as LBLP is an internationally agreed research priority (Costa Lda et al. 2013).

In some key areas of musculoskeletal pain research, there has been a move away from considering all pain patients as the same or a 'one size fits all approach' and towards stratified care that develops and tests ways to better match patients to treatment (Foster et al. 2013). There are specific treatments (principally medications) available to patients with neuropathic pain in primary care and neuropathic pain medications are advocated for patients with sciatica. In the background literature review presented in Chapter 1, published research reports that despite the availability of specific medications, patients with neuropathic pain are often under-treated. In part, under-treatment may be because detecting neuropathic pain with reasonable certainty is difficult in clinical practice, the causal mechanisms are complex and there is no gold standard for identifying cases of neuropathic pain. Despite difficulties in identifying patients with neuropathic pain there is some agreement that cases can be identified by clinical history and examination and by using validated neuropathic case ascertainment tools. This agreement is important because identifying cases is a necessary starting point in the epidemiological research of patients with neuropathic pain. Understanding the prevalence, characteristics, clinical course, factors contributing to the prognosis of, and pain medication use in LBLP patients with neuropathic pain may help to inform patients and clinicians of the likely nature of the pain and inform future research leading to the provision of timely, targeted treatments.

2.2 Aims and Objectives

The overall aim of the research in this thesis is to investigate the epidemiology, in terms of the prevalence, baseline characteristics, clinical course, factors contributing to the prognosis of, and the pain medication use in LBLP patients with neuropathic pain who consult with their general practitioner (GP) in primary care.

2.2.1 Objectives

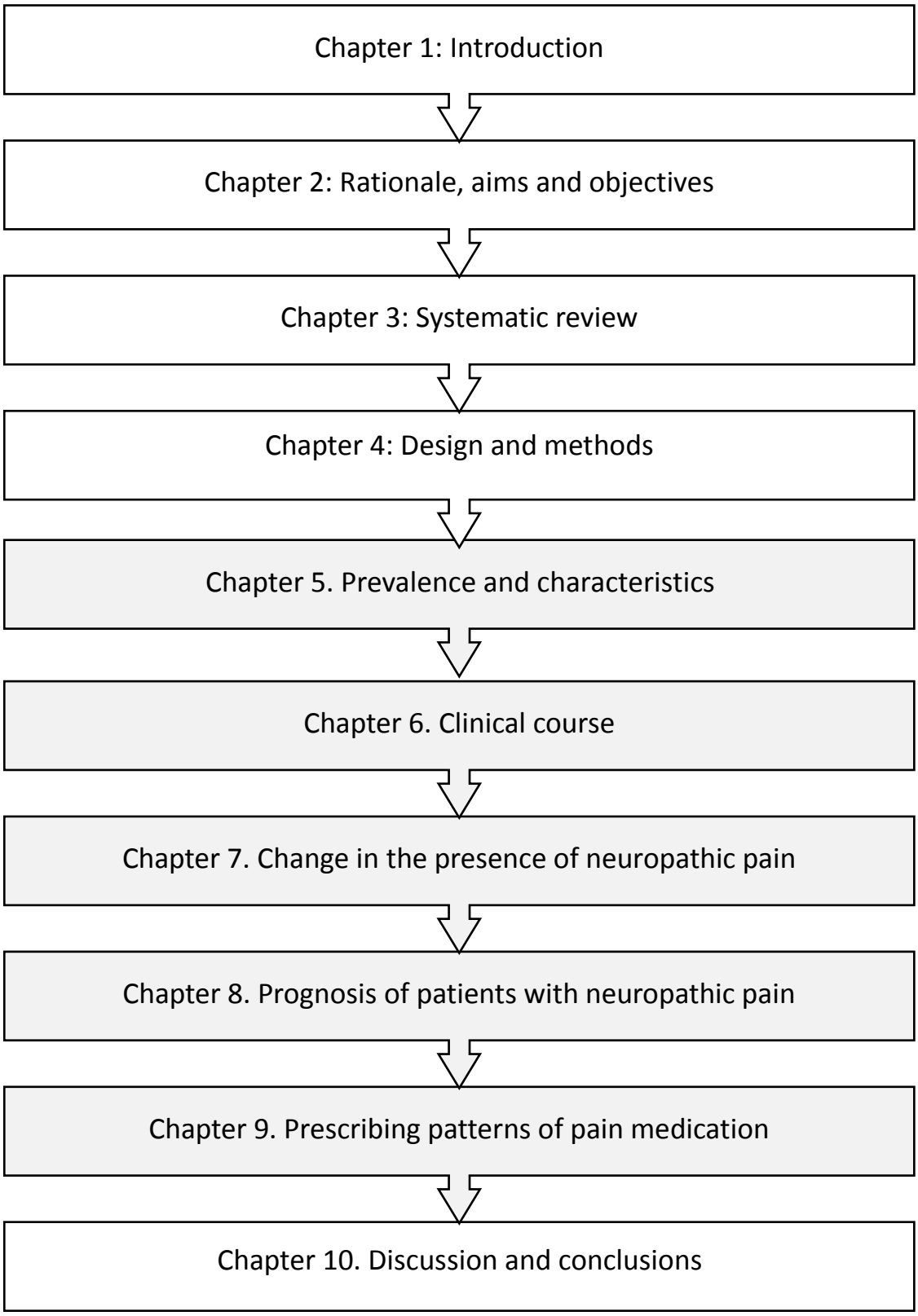
The specific objectives of this thesis are:

1. To systematically review the literature on the prevalence, clinical course and prognosis of LBLP patients with neuropathic pain in primary care.
2. To provide point prevalence estimates of neuropathic pain in a primary care population.
3. Describe the characteristics of LBLP primary care patients with neuropathic pain compared to those without.
4. To compare the clinical course of LBLP patients with neuropathic pain at baseline compared to those without.
5. To describe the change in neuropathic pain over time in LBLP patients with and without neuropathic pain at baseline.
6. To investigate the overall prognosis of LBLP patients with neuropathic pain, in terms of clinical course and exploratory prognostic factor research.
7. To describe the pain medications prescribed in primary care to LBLP patients with neuropathic pain, and to identify patients with refractory neuropathic pain.

2.3 Outline

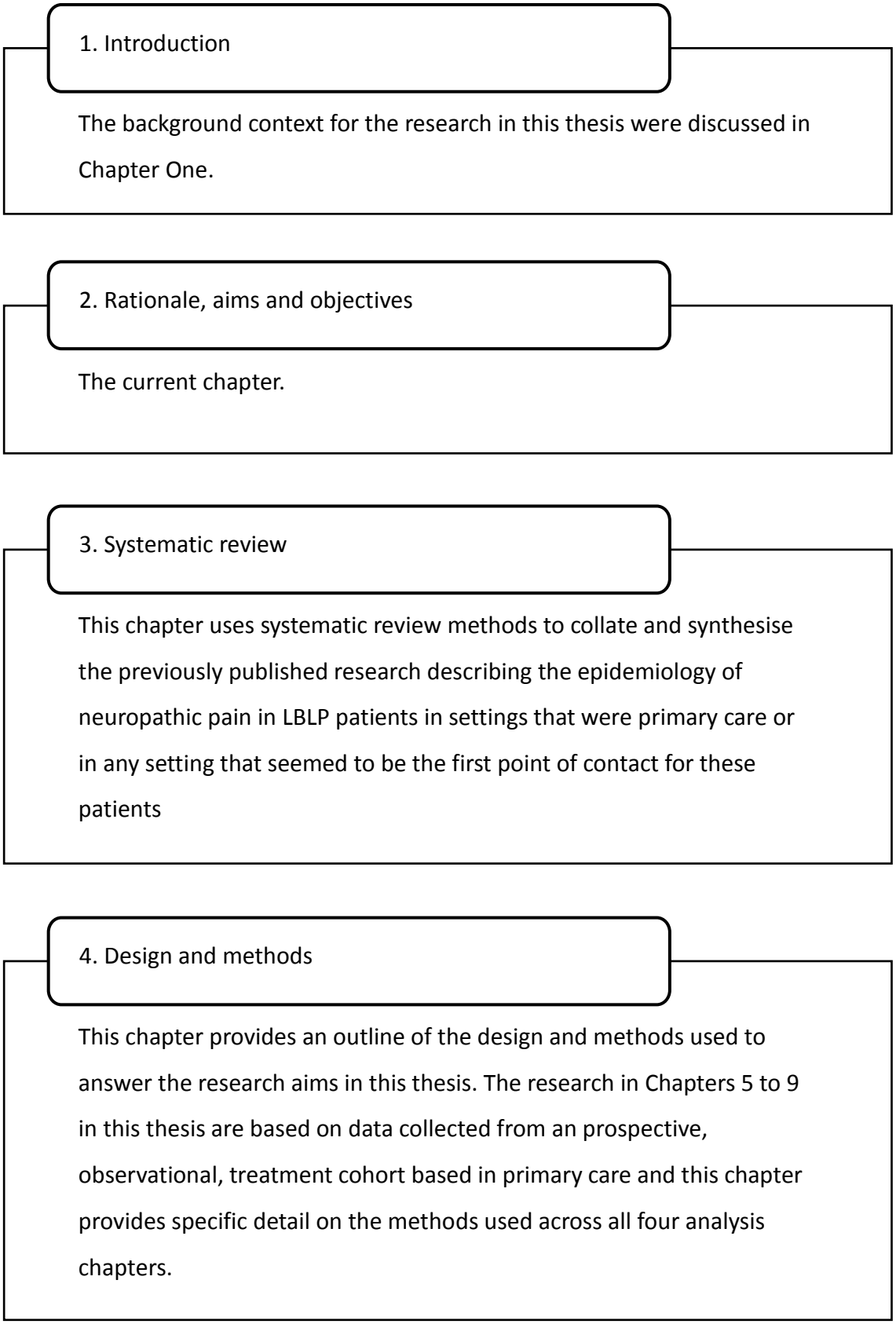
This thesis is divided into the following ten chapters: Introduction, rationale, aims and objectives, systematic review, study design and methods, prevalence and baseline characteristics, clinical course, change in the presence of neuropathic pain, prognosis of LBLP patients with persistent neuropathic pain, pain medication use and discussion and conclusions (Figure 2.1 illustrates the structure of this thesis). Chapters 5 to 9 provide a report of the epidemiological analysis carried out for this thesis, the research in Chapter 5 reports on findings from research using cross-sectional data and the research in Chapters 6 to 9 report on findings from research using longitudinal data. The series of analyses in Chapter 5 (prevalence and baseline characteristics), 6 (clinical course) and 8 (prognosis of LBLP patients with neuropathic pain) was linear, with the conclusions of the preceding chapter informing the next. The descriptive analysis in Chapter 7 (change in the presence of neuropathic pain) was completed concurrently to that in Chapters 5 and 6, the findings of Chapter 7 also informed the analysis in Chapter 8. Electronic prescribing records from participating general practices were prepared and coding was generated to identify pain medications in Chapter 9 (prescribing patterns of pain medication) concurrent to research in preceding chapters, with findings of analyses in earlier chapters informing the analysis plan in this chapter. Finally, Chapter 10 presents the combined findings and implications of this series of analyses. Figure 2.2 below provides a brief outline of each chapter.

Figure 2.1 Flow diagram summarising thesis structure



Shaded boxes highlight research based on epidemiological analysis of a prospective cohort of LBLP patients consulting in primary care.

Figure 2.2 Outline of chapters in this thesis



5. Prevalence and characteristics

This chapter describes the prevalence of LBLP patients with neuropathic pain and compares the characteristics of patients with and without neuropathic pain at baseline. Cases of neuropathic pain in this chapter were identified based on two approaches using three definitions.

6. Clinical course

The research in this chapter compares the clinical course of LBLP patients with neuropathic pain at baseline in terms of pain intensity and leg and back-related disability over short, intermediate and long-term follow-up compared to those without. As with research in the previous chapter, the results in this chapter are reported for two approaches and three definitions of neuropathic pain.

7. Change in the presence of neuropathic pain

This chapter describes the change in the presence of neuropathic pain over short, intermediate and long-term follow-up and identifies a sub-group of patients with persistent neuropathic pain. Patients with neuropathic pain and persistent neuropathic pain were identified based on one approach and definition.

8. Prognosis of patients with neuropathic pain

In this chapter, the characteristics and clinical course of patients with persistent neuropathic pain compared to those without are investigated. Potential prognostic factors are identified and the prognostic value of certain characteristics of LBLP patients with neuropathic pain that may be associated with the outcome of interest, persistent neuropathic pain are reported in what is exploratory prognostic factor research.

9. Prescribing patterns of pain medication

In this chapter, a description of the pain medications prescribed in primary care to LBLP patients with neuropathic pain (based on two approaches and three definitions) is reported. The chapter then describes the proportion of LBLP patients with refractory neuropathic pain based on an understanding of the results reported in Chapters 6 (clinical course) and 7 (change in the presence of neuropathic pain).

10. Discussion and conclusions

This final chapter collates and critically re-examines the findings from each element of the analyses presented in this thesis. The implications for future research are discussed and suggestions of how this thesis can inform clinical practice are provided.

Shaded boxes highlight research based on epidemiological analysis of a prospective cohort of LBLP patients consulting in primary care.

2.4 Summary

This chapter has presented the rationale, aims and objectives underlying the research in this thesis, and an outline and a brief summary of subsequent chapters are provided. The following chapter will describe a systematic review of the prevalence, characteristics and prognosis of LBLP patients with and without neuropathic pain, designed to investigate the current gap in the knowledge base.

Chapter Three. Neuropathic pain in low back-related leg pain: prevalence, characteristics and prognosis. A systematic review of the literature.

3.1 Introduction

Current pain research has predominantly been conducted in specialist pain centres based often in tertiary care. It is likely that populations drawn from these setting are systematically different to primary care patients which limits the generalisability of these findings to patients who consult in primary care. The prevalence of neuropathic pain in LBLP patients remains unclear, as does its clinical course and factors associated with its prognosis, especially in primary care. This chapter presents the rationale for, methods and findings of a systematic review of observational studies examining the prevalence, clinical course and prognostic indicators of neuropathic pain in LBLP patients consulting in settings identified as the first point of contact for this population, either in primary care or specialist clinics or services.

3.2 Aims

The primary aim of this systematic review was to synthesise currently available knowledge about the epidemiology of neuropathic pain in patients consulting with LBLP. The specific objectives of the review were to collate, critically appraise and synthesise the current published evidence on the prevalence, characteristics and prognosis of neuropathic pain in LBLP patients who consulted in settings that seemed to be the first point of contact for this population.

3.3 Methods

3.3.1 Protocol registration

A protocol of this systematic review was registered and can be accessed on the PROSPERO international prospective register of systematic reviews (through the web address http://www.crd.york.ac.uk/PROSPERO/ using the registration number CRD42015023388).

3.3.2 Search strategy

Electronic databases MEDLINE, EMBASE, CINAHL, AMED, Web of Science Core Collection and TRIP were searched from inception of each database to August 2015 and the search was re-run in January 2018 to identify any new publications as detailed in Table 3.1. The search was not restricted to specific languages. The search strategy was developed in consultation with information specialists and used all key words and MeSH terms to explore the most important key areas: LBLP, neuropathic pain, and epidemiology. Appendix A1 presents the full search strategy for all six electronic databases. A supplementary search was carried out by bibliography screening and citation tracking of included articles (Hayden et al. 2009), relevant systematic reviews and original articles of case identification tools (Bennett 2001, Bouhassira et al. 2005, Freynhagen et al. 2006a). A search of the grey literature was carried out, seeking unpublished research in doctoral theses and from conference proceedings, via the internet search engines Google Scholar and OpenGrey.

Table 3.1 Details of electronic databases searched

	Initial search			**2nd Search**		
Database	Interface	Date of search	Date ranges*	Interface	Date of search	Date ranges
Medline	HDAS	28/07/2015	1964 to date of search	OvidSP	02/01/2018	2015 to date of 2nd search
CINAHL	HDAS	27/07/2015	1981 to date of search	EBSCO	03/01/2018	July 2015 to date of 2nd search
EMBASE	OvidSP	03/08/2015	1974 to 2015 week (30)	OvidSP	03/01/2018	2015 to date of 2nd search
AMED	OvidSP	03/08/2015	1985 to 2015 month (8)	EBSCO	03/01/2018	August 2015 to date of 2nd search
Web of Science Core Collection	Web of Science	05/08/2015	1970 to date of search	Web of Science	02/01/2018	2015 to date of 2nd search
TRIP	Tripdatabase.com	05/08/2015	n/a	Tripdatabase.com	02/01/2018	n/a

*All databases were searched in a range of dates, from inception to the date of search

3.3.2 Study selection

Eligibility criteria to assist with study selection were developed for this review, an itemised description of the inclusion and exclusion criteria can be found in Table 3.2. The study design, participants (for example, the age of the participants), presence or absence of pain with neuropathic characteristics, clinical setting in which the study was carried out and the study outcomes were all considered for eligibility.

Table 3.2 Eligibility criteria for study selection

Published studies were included if they fulfilled any of the following criteria:

• Cohort study, case control, cross-sectional study designs available as full text
• Human participants, over 18 years
• Clearly defined groups of patients with and without neuropathic pain (for example, through using neuropathic case ascertainment tools, clinical history and clinical examination)
• Participants with low back-related leg pain
• Primary care, or clinical settings identified as the first point of contact for patients with low back-related leg pain where assessment and treatment of the population could be applied in primary care. Including:
  ○ occupational settings
  ○ physiotherapy outpatients, general practice, osteopathic or chiropractic clinics
  ○ secondary care
• Data reporting prevalence or incidence, clinical course of the condition, characteristics associated with prognosis of the condition (for example, severity of pain, duration of pain, back/leg pain disability)

Published studies were excluded if they fulfilled any of the following criteria:

- Intervention studies (e.g. RCTs), case studies, small case series, systematic reviews, guidelines and medical reference
- Animal subjects
- Specific neuropathic pain conditions. Including:
    - diabetes, cancer, HIV, multiple sclerosis, Guillain Barre syndrome, spinal cord injuries
- Low back pain patients where related leg pain is not clearly defined
- Populations with specific back pain conditions. Including:
    - pregnant women, post-surgical patients, ankylosing spondylitis, rheumatoid arthritis, lumbar spinal stenosis, herniated discs, failed back surgery syndrome, osteoporosis, serious spinal pathology (cauda equina, malignancy, fractures, spinal infection)
- Other settings. Including:
    - Settings where spinal surgery, spinal cord stimulation, caudal epidural or facet joint injections or spinal nerve root blocks were carried out

Abbreviations: HIV, human immunodeficiency virus. RCT, randomised controlled trial.

3.3.3 Data extraction

All citations identified from the electronic databases were directly imported into an online reference management system (Endnote X7.4) and duplicates were removed. Eligible studies were selected on title first by one reviewer (SH) at which point citations clearly not relevant based on the eligibility criteria were removed. Where there was insufficient information in the title, the abstract was retrieved. Screening of titles with abstracts was completed by two independent reviewers (SH and SS). Full papers were retrieved and assessed if the abstract provided insufficient information. Disagreements were resolved by consensus. Two independent reviewers (SH and SS, KK or KD) extracted data from eligible papers using a bespoke data extraction form. Collected

information included: study name, authors and publication year; publication language; study design; study population; sampling methods; definition of LBLP, participant characteristics; definition of neuropathic pain; method of case ascertainment for neuropathic pain; description of prevalence; characteristics associated with neuropathic pain (including characteristics of pain, disability, psychological characteristics, quality of life scores, clinical examination and medication use); clinical course of condition and factors associated with prognosis. A full copy of the data extraction form can be found in Appendix A2. Authors were contacted for further data or clarification where required.

3.3.4 Risk of bias (quality assessment)

Two quality assessment tools were used in this review (Hoy et al. 2012b, Hayden et al. 2013). One to appraise the evidence on prevalence (Hoy et al. 2012b) and one to appraise the evidence on characteristics and prognosis (Hayden et al. 2013). Hoy et al., (2012) developed a tool to assess risk of bias in prevalence studies. This tool includes ten specific items, four of which are related to external validity and six related to internal validity, with each item rated as being either at low or high risk of bias. In this review, in the case where there was insufficient information for a judgement to be made for a particular item, the item was assigned as high risk of bias. Each included study was then assigned an overall risk of study bias as 'low', 'moderate' or 'high'. Studies with eight or more items scored as low risk were considered overall to be of 'low risk of bias', those with six to seven items scored as low risk were considered overall to be of 'moderate risk of bias', and those with five or fewer items scored as

low risk were considered overall to be of 'high risk of bias'. This way of scoring the overall risk of bias has been done before by previous systematic reviews (Aminde et al. 2016, Gupta and Simpson 2015, Usenbo et al. 2015).

The Quality in Prognosis Study (QUIPS) tool (Hayden et al. 2013) was used to appraise individual studies providing data on characteristics and prognosis. This tool investigates six domains where there is a risk of bias: study participation; study attrition; measurement of prognostic factors; measurement of outcomes; measurement of and controlling for confounding variables; statistical analysis and reporting. The different domains were assigned as having 'low', 'moderate', 'high' or that the reviewer was unsure of the risk of bias, or that the domain was not relevant. The study was then assigned as having 'low', 'moderate' or 'high' risk of bias. The reviewers were not blinded to authors, institutions, or journal of publication, this was applicable for both tools. Disagreements were resolved by discussion and consensus between the two reviewers. All studies, regardless of their quality were included for critical appraisal and synthesis.

3.3.5 Data analysis

For each of the studies identified, data on prevalence, characteristics and prognosis were extracted. It was anticipated that studies to be included in this review would have considerable variability in participants, in the approaches used to define neuropathic pain and in the study settings and that this would make it unlikely that the quantitative data from studies could be pooled together into single summary estimates. Therefore, a narrative synthesis was anticipated (and subsequently

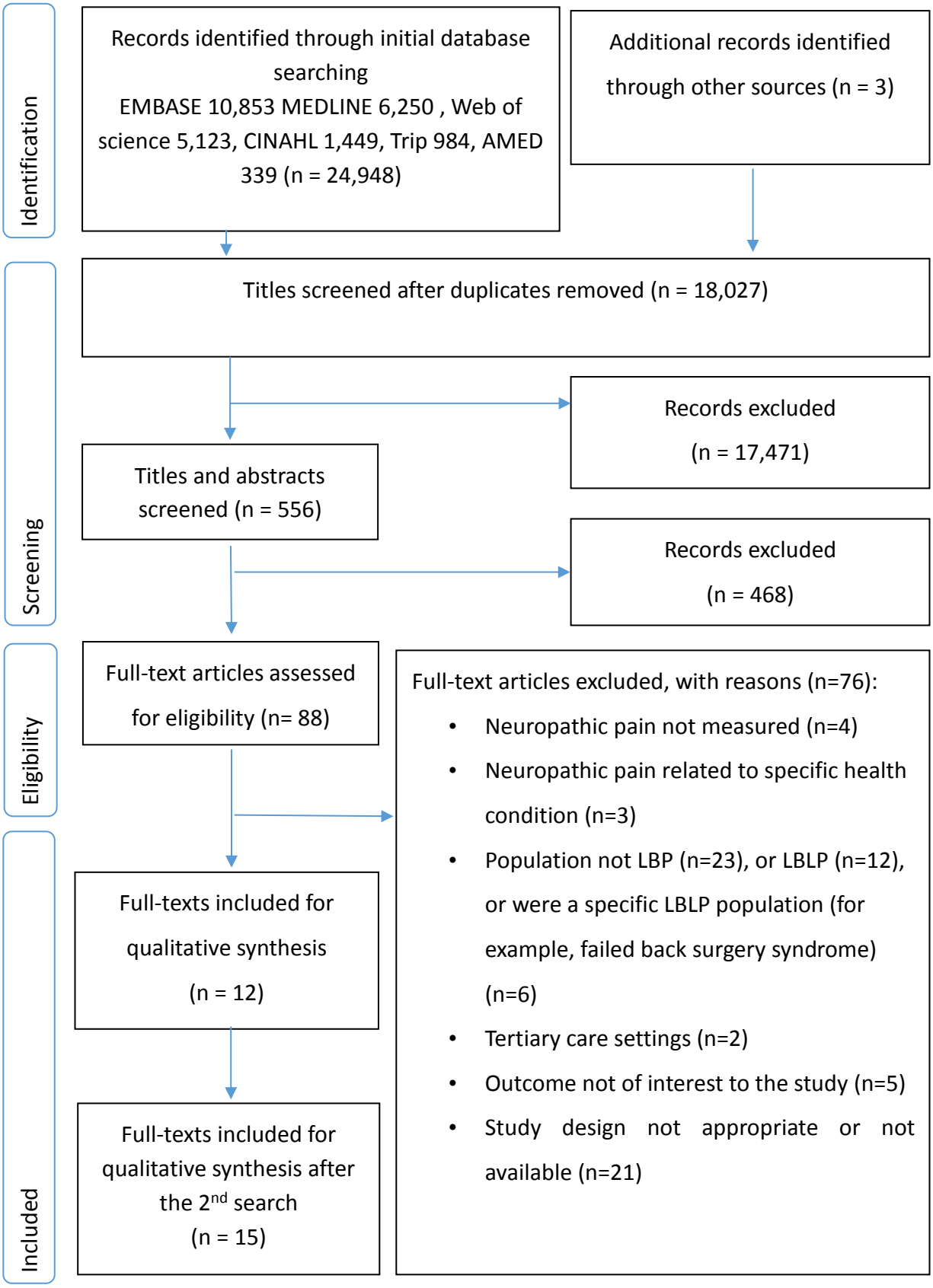
conducted), with textual description of studies and tabulation of results (Deeks et al.). An exploration of robustness of the synthesis and an exploration of relationships between and within studies formed part of this narrative review.

3.4 Results

3.4.1 Studies identified

The initial search (July/August 2015) of electronic databases yielded 24,948 articles (Figure 3.1 shows a flow chart adapted from the PRISMA flow chart (Moher et al. 2009)). An additional three articles were identified through other sources; two titles were retrieved from citation tracking of relevant systematic reviews and of original articles of case identification tools, the third title was identified through citation tracking of included articles. 88 full text articles were assessed for eligibility, just under half (n=41) were excluded because data could not be extracted on LBLP patients or because the population were patients with LBLP conditions clearly requiring specialist care (for example; failed back surgery syndrome), two articles were excluded because the population described consulted in tertiary care centres and were not directly comparable to primary care samples (Figure 3.1 summarises all reasons for excluded studies). Twelve full text articles from the first search were included in the review, with a further three full text articles identified in the 2nd search (Appendix A3 shows a flow chart of the 2nd systematic search and study selection). All fifteen included articles underwent quality assessment and data extraction.

Figure 3.1. Flow chart of systematic search and study selection (adapted from the PRISMA flow chart) (Moher et al., 2009)



3.4.1.1 Summary of included studies

A summary of the included studies is presented in Table 3.3. None of the studies included in this systematic review directly aimed to estimate prevalence or describe the characteristics of LBLP patients with neuropathic pain. However, it was possible to extrapolate data to estimate prevalence of neuropathic pain in LBLP patients in ten of the studies (Attal et al. 2011, Ouédraogo et al. 2012, Schafer et al. 2011, Walsh et al. 2012, Morsø et al. 2011, Uher and Bob 2013, Beith et al. 2011, Hüllemann et al. 2017, Orita et al. 2016, Gierthmühlen et al. 2017). Eleven studies reported on characteristics (Beith et al. 2011, Freynhagen et al. 2008, Morsø et al. 2011, Schafer et al. 2011, Tutoglu et al. 2015, Uher and Bob 2013, Walsh and Hall 2009, Smart et al. 2012a, Mahn et al. 2011, Defrin et al. 2014, Gierthmühlen et al. 2017), and from the three studies that provided longitudinal data, it was possible to derive information on prognosis from two studies (Morsø et al. 2011, Hüllemann et al. 2017). A total of 50,769 patients were included in all 15 studies. The majority (9 out of 15) of samples had less than 100 patients, one study had a sample size of 45,457 (Hüllemann et al. 2017). There was wide variability in the characteristics of the LBLP patient population in the included studies, with mixed pain severity and duration, and the classification of LBLP by some studies was closely associated with the definition of neuropathic pain. Two studies described characteristics of neuropathic pain in LBLP without a comparison group relevant to the study (Mahn et al. 2011, Smart et al. 2011), one study described characteristics of patients without neuropathic pain who may have included LBP patients without leg pain (Gierthmühlen et al. 2017). One study described

characteristics with an alternative comparison group (Defrin et al. 2014), neuropathic pain in LBLP patients with or without allodynia. These four studies were included in the review because of the relevance of the reported characteristics. There was some consistency in the age and the proportion of females to males across the studies (samples were predominantly female).

3.4.1.2 Case definition of neuropathic pain

Neuropathic pain was most commonly identified using case ascertainment tools, either in isolation (Beith et al. 2011, Tutoglu et al. 2015, Uher and Bob 2013, Morsø et al. 2011, Ouédraogo et al. 2012, Hüllemann et al. 2017, Orita et al. 2016) or in addition to clinical history and examination (Attal et al. 2011, Schafer et al. 2011, Walsh and Hall 2009, Gierthmühlen et al. 2017). Three studies (Freynhagen et al. 2008, Defrin et al. 2014, Mahn et al. 2011) used their definition of LBLP to assume a neuropathic component, so all patients in these studies were considered to have neuropathic pain. All studies were published since the IASP redefinition and grading system for neuropathic pain (Treede et al. 2008) and this was cited by six out of the fifteen studies (Attal et al. 2011, Defrin et al. 2014, Freynhagen et al. 2008, Smart et al. 2012a, Schafer et al. 2011, Orita et al. 2016). With reference to the IASP grading system, the most common working hypothesis of neuropathic pain was 'probable' (Attal et al. 2011, Freynhagen et al. 2008, Schafer et al. 2011). Three studies defined neuropathic pain using a mechanisms based classification, without specific reference to the IASP definition (Walsh and Hall 2009, Uher and Bob 2013, Smart et al. 2012a). One study defined neuropathic pain with reference to the original IASP definition of neuropathic

pain (‘pain initiated or caused by a primary lesion or dysfunction in the nervous system’) (Tutoglu et al. 2015).

Table 3.3 Summary of all fifteen studies included in the systematic review

Study author, date and country	**Study design**	**LBLP Population**	**Population** *(Number in sample, proportion of male, mean age ((years) (standard deviation))*	**Comparator group: LBLP patients with vs without neuropathic pain**	**Method of measuring neuropathic pain**	**Grade of neuropathic pain (Treede et al. 2008)**	**Setting**
Attal et al. (2011b), France	Cross-sectional	Mixed* LBLP > 3 months symptom duration and VAS ≥4/10 (QTSFD† groups 2 to 4)	N = 92 41% M Age: 54 (14)	Yes	DN4	QTSFD group 4: Probable	MDT pain clinics or rheumatology centres
Beith et al. (2011), UK	Cross-sectional	Mixed* LBLP	N=227 (NR)% M Age: NR	Yes	PainDETECT	Possible	Physiotherapy referrals in primary care and secondary care

Study author, date and country	Study design	LBLP Population	Population *(Number in sample, proportion of male, mean age ((years) (standard deviation))*	Comparator group: LBLP patients with vs without neuropathic pain	Method of measuring neuropathic pain	Grade of neuropathic pain (Treede et al. 2008)	Setting
Defrin et al. (2014), Israel	Case control	Sciatica > 3 months with radicular pain into the leg**	N = 74 47% M Age: 66 (NR)	No (neuropathic pain in LBLP with vs without allodynia)	Clinical history including imaging and electrophysiology	Probable	Pain clinic
Freynhagen et al. (2008), Germany	Case control	Sciatica (chronic unilateral leg pain)	Radicular pain: N=15 42% M Age: 54 (16)	Yes	Clinical history, examination and imaging/ electrophysiology where indicated	Not defined	Pain medicine, neurology and neurosurgery setting

Study author, date and country	Study design	LBLP Population	Population *(Number in sample, proportion of male, mean age ((years) (standard deviation))*	Comparator group: LBLP patients with vs without neuropathic pain	Method of measuring neuropathic pain	Grade of neuropathic pain (Treede et al. 2008)	Setting
			Pseudoradicular pain: N=12, 44%M Age: 52 (16)				
Gierthmühlen et al. (2017), **Germany**	Cross-sectional	LBLP > 3 months	N=51 (51)%M, Age: 61 (12)	Yes	Clinical history, examination, MRI imaging and separately PainDETECT	Not defined	Department of Neurology after consulting from local medical practices or in response to an

Study author, date and country	Study design	LBLP Population	Population *(Number in sample, proportion of male, mean age ((years) (standard deviation))*	Comparator group: LBLP patients with vs without neuropathic pain	Method of measuring neuropathic pain	Grade of neuropathic pain (Treede et al. 2008)	Setting
							announcement in a local newspaper
Hüllemann et al. (2017), **Germany**	Cross-sectional with follow-up data	Mixed* LBP, categorised into 4 groups by pain location, 3 out of 4 groups with LBLP‡	Group 2: N=30,000 (NR)% M Age: 58 (15) Group 3: N=12,988 (NR)% M Age: 54 (15) Group 2: N=2,469	No	PainDETECT	Possible	862 primary care outpatient centres

Study author, date and country	Study design	LBLP Population	Population *(Number in sample, proportion of male, mean age ((years) (standard deviation))*	Comparator group: LBLP patients with vs without neuropathic pain	Method of measuring neuropathic pain	Grade of neuropathic pain (Treede et al. 2008)	Setting
			(NR)% M Age: 54 (15)				
Mahn et al. (2011), Germany	Cross-sectional	Sciatica **	N=2094 42% M Age: 59 (14)	No	History, clinical assessment, leg pain worse than back pain	Probable	450 outpatient centres (primary and secondary care)
Morsø et al. (2011), Denmark	Cross-sectional with follow up data	Mixed* LBLP > 3 months and <12months	N=145 39% M Age: 50 (15)	Yes	PainDETECT	Possible	Outpatient spine centre in secondary care

Study author, date and country	Study design	LBLP Population	Population *(Number in sample, proportion of male, mean age ((years) (standard deviation))*	Comparator group: LBLP patients with vs without neuropathic pain	Method of measuring neuropathic pain	Grade of neuropathic pain (Treede et al. 2008)	Setting
Orita et al. (2016)	Cross-sectional	Mixed* LBP, categorised into by pain location	Neuropathic: N = 737 (47)%M Nociceptive: N = 1067 (48)%M	Yes	Japanese neuropathic screening questionnaire	Not defined	137 Medical institutions (orthopaedic hospitals, general hospitals and university hospitals)
Ouédraogo et al. (2012), **Burkina Faso**	Cross-sectional	Mixed* LBLP	N = 66 (NR)%M Age: NR	Yes	DN4	Not defined	Rheumatology, neurology and neurosurgery clinics

Study author, date and country	Study design	LBLP Population	Population *(Number in sample, proportion of male, mean age ((years) (standard deviation))*	Comparator group: LBLP patients with vs without neuropathic pain	Method of measuring neuropathic pain	Grade of neuropathic pain (Treede et al. 2008)	Setting
Schafer et al. (2011), Germany	Cross-sectional follow up data	Mixed* LBLP > 6 weeks and NRS >3/10 §	N = 74 40% M Age: 48 (13)	Yes	LANSS and clinical assessment to determine neural related leg pain classification	Not defined	MDT pain clinics
Smart et al. (2012a), UK & Ireland	Cross-sectional	Mixed* LBP +/- leg pain‖	N = 474 44% M Age: 44 (NR)	No	Clinical indicators derived from a mechanisms based classification system	Not defined	4 hospital sites: back pain clinics (assessments done by physiotherapists)

Study author, date and country	Study design	LBLP Population	Population *(Number in sample, proportion of male, mean age ((years) (standard deviation))*	Comparator group: LBLP patients with vs without neuropathic pain	Method of measuring neuropathic pain	Grade of neuropathic pain (Treede et al. 2008)	Setting
Tutoglu et al. (2015), **Turkey**	Case control	Sciatica (lumbar discopathy on neuroimaging)	N=73 40% M Age: for sciatica group with neuropathic pain: 53 (10), For sciatica group without neuropathic pain: 50 (7)	Yes	DN4	Not defined	Physical medicine and rehabilitation outpatient clinic

Study author, date and country	Study design	LBLP Population	Population *(Number in sample, proportion of male, mean age ((years) (standard deviation))*	Comparator group: LBLP patients with vs without neuropathic pain	Method of measuring neuropathic pain	Grade of neuropathic pain (Treede et al. 2008)	Setting
Uher and Bob (2013), **Czech Republic**	Cross-sectional	Sciatica (L4, L5 or S1 radicular syndrome & lumbar disc herniation or foraminal stenosis on neuroimaging)	N=66 42% M Age: 58 (NR)	Yes	PainDETECT (Czech version)	Not defined	Neurology inpatients
Walsh and Hall (2009), **Ireland**	Cross-sectional	Mixed* LBLP§	N=45 49% M Age: 46 (11)	Yes	S-LANSS and clinical assessment to determine	Not defined	Back pain clinic

Study author, date and country	Study design	LBLP Population	Population *(Number in sample, proportion of male, mean age ((years) (standard deviation))*	Comparator group: LBLP patients with vs without neuropathic pain	Method of measuring neuropathic pain	Grade of neuropathic pain (Treede et al. 2008)	Setting
					neuropathic related leg pain		

Abbreviations: DN4, Doleur Neuropathique en 4. LANSS, Leeds Assessment of Neuropathic Symptoms and Signs. LBLP, low back-related leg pain. NR, not reported. NRS, numerical rating scale. M, male. MDT, multi-disciplinary team. MRI, magnetic resonance imaging. L4, L5, S1, lumbar spinal nerve roots. QTSFD, Quebec task force classification of spinal disorder. S-LANSS, Self-report version of the Leeds Assessment of Neuropathic Symptoms and Signs. VAS, visual analogue scale.

* Mixed LBLP: heterogeneous samples of LBP (where leg pain is clearly defined) or LBLP that include both clinical diagnosis of sciatica and referred leg pain.

† QTSFD, classified as group 2 to 4: Group 2, pain in the lumbar area with proximal radiation (i.e., to lower limb, but not beyond the knee). Group 3, pain in the lumbar area radiating below the knee and no neurological signs. Group 4, pain in the lumbar area radiating towards the foot in a dermatomal distribution, associated with sensory deficits or other neurological signs.

‡ LBLP patients were classified into group 2 to 4. Group 2, pain in the lumbar area radiating to above knee. Group 3, pain in the lumbar region radiating to below knee (but not the foot). Group 4, pain in the lumbar region radiating to at least one foot.

§ Diagnostically classified into one of four groups, neuropathic sensitisation, denervation, peripheral nerve sensitisation or musculoskeletal.

‖ Diagnostically classified into one of three groups, peripheral neuropathic pain (PNP), central neuropathic pain and nociceptive pain. PNP was made up of 91% LBLP and 9% predominant low back pain; central neuropathic and nociceptive pain were predominantly low back pain (61% and 82% respectively).

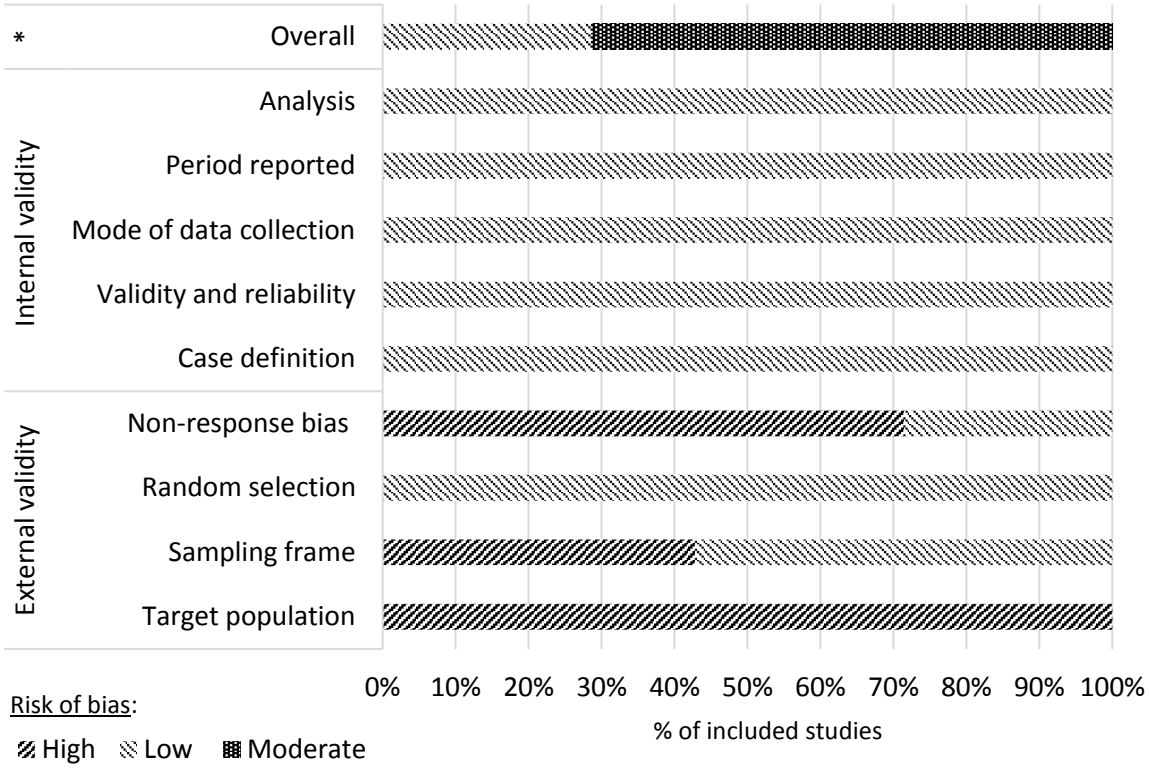
** In this study, radicular pain was considered synonymous to neuropathic pain.

3.4.2 Prevalence

3.4.2.1 Quality assessment of prevalence studies

All ten of the studies providing a prevalence estimate for of neuropathic pain in LBLP underwent quality assessment by two independent reviewers using a tool specific to risk of bias for prevalence studies (Hoy et al. 2012b). A third independent reviewer was necessary to determine the risk of bias of one domain in four of the studies where agreement could not be reached by the two reviewers. External validity in the included studies was at higher risk of bias (see Table 3.4 for a summary and Appendix A4 for the full results of the quality assessment process) for nine out of ten studies compared to the domains covering internal validity. Six out of the ten studies were deemed to be of moderate risk of bias (Attal et al. 2011, Orita et al. 2016, Ouédraogo et al. 2012, Schafer et al. 2011, Uher and Bob 2013, Walsh and Hall 2009), one study was at high risk of bias (Gierthmühlen et al. 2017). Further research is likely or very likely to have an important impact on the confidence in the prevalence estimate and may also change the estimate derived from each of these studies (Hoy et al. 2012b). Three of the studies (Beith et al. 2011, Morsø et al. 2011, Hüllemann et al. 2017) were considered to be of low risk of bias where further research is very unlikely to change the confidence in the reported estimate.

Table 3.4. Summary of quality assessment (described as risk of bias) of the ten included studies used to derive prevalence



3.4.2.2 Prevalence estimates in included studies

Prevalence estimates were derived from a total of 12,551 patients in the ten studies (Table 3.5 summarises the prevalence of neuropathic pain in the studies included in this review). None of the studies reported confidence intervals for the prevalence estimates and all but two studies (Hüllemann et al. 2017, Orita et al. 2016) utilised small samples, one of which was at low risk of bias (Hüllemann et al. 2017). Across the studies, the prevalence of neuropathic pain in LBLP varied from 5% to 80%. The prevalence of neuropathic pain in LBLP patients varied from 5% in patients with referred leg pain who were referred to a neurology department after consulting in a primary care setting, or who responded to an announcement in a local newspaper

(Gierthmühlen et al. 2017), to 80% in a sample of patients with LBLP associated with neurological signs who were recruited from either pain clinics or rheumatology settings . The prevalence of neuropathic pain in LBLP patients estimated using PainDETECT to identify cases of "possible" neuropathic pain, in studies at low risk of bias (Hüllemann et al. 2017, Beith et al. 2011, Morsø et al. 2011) ranged from 19% to 22%. In two studies using used samples that categorised patients in part or entirely based on location of pain in the leg (Attal et al. 2011, Hüllemann et al. 2017), neuropathic pain was less prevalent in patients with pain above the knee (15% to 20%) compared to those with pain below the knee (25% to 80%). The prevalence of neuropathic pain was higher in populations of LBLP with sciatica (Uher and Bob 2013, Attal et al. 2011, Gierthmühlen et al. 2017) compared to mixed populations of LBLP (i.e., sciatica and referred pain) (for example, (Beith et al. 2011, Morsø et al. 2011, Hüllemann et al. 2017)). Not all patients with a clinical diagnosis of sciatica had "possible" neuropathic pain based on PainDETECT and a few (5%) diagnosed with referred leg pain had a neuropathic type of pain. PainDETECT (Freynhagen et al. 2006a) was the most commonly used tool to derive an estimate of prevalence (Gierthmühlen et al. 2017, Hüllemann et al. 2017, Morsø et al. 2011, Uher and Bob 2013, Beith et al. 2011), estimates were no higher than 46% (for patients with chronic sciatica) (Uher and Bob 2013). Neuropathic pain in LBLP patients identified using the Japanese neuropathic screening questionnaire was highly prevalent (78%) (Orita et al. 2016), similarly in four out of five patients with a clinical diagnosis of sciatica had neuropathic pain as identified using the DN4 (Attal et al. 2011).

Table 3.5 Studies showing prevalence of neuropathic pain in LBLP, grouped by method of defining neuropathic pain

Study	Numerator	Denominator (N)	Prevalence of neuropathic pain (%)*
Clinical examination			
Gierthmühlen et al. (2017)	Clinical diagnosis of sciatica and relevant findings on MRI	LBLP (n=51)	37
DN4			
Attal et al. (2011)	DN4 ≥ 4	LBLP (n=92)	49
		QTSFD† group 2 (n=27)	15
		QTSFD† group 3 (n=38)	39
		QTSFD† group 4 (n=27)	80
Ouédraogo et al. (2012)	DN4 ≥ 4	LBLP (n=66)	61
LANSS/ s-LANSS			
Schafer et al. (2011)	LANSS ≥12 and clinical examination confirming neuropathic pain	LBLP (n=74)	26
	Clinical examination confirming neuropathic pain but with LANSS <12	LBLP (n=74)	47
Walsh and Hall (2009)	S-LANSS ≥12 and clinical examination confirming neuropathic pain	LBLP (n=45)	33
	Clinical examination confirming neuropathic pain but with S-LANSS <12	LBLP (n=45)	40

Study	Numerator	Denominator (N)	Prevalence of neuropathic pain (%)*
PainDETECT			
Gierthmühlen et al. (2017)	"Possible" neuropathic pain component	Clinical diagnosis of sciatica and relevant findings on MRI (n=19)	31
	"Possible" neuropathic pain component	Referred leg pain (n=42)	5
Hüllemann et al. (2017)	"Possible" neuropathic pain component	LBLP (n=45,457)	22
	"Possible" neuropathic pain component	Group 2, pain in the lumbar area radiating to above knee (n=30,000)	20
	"Possible" neuropathic pain component	Group 3, pain in the lumbar region radiating to below knee (but not the foot) (n=12,988)	25
	"Possible" neuropathic pain component	Group 4, pain in the lumbar region radiating to at least one foot (n=2,469)	34
Morsø et al. (2011)	"Possible" neuropathic pain component	LBLP (n=145)	19
	"Uncertain" neuropathic pain classification	LBLP (n=145)	26
Uher and Bob (2013)	"Possible" neuropathic pain component	Acute and sub-acute sciatica (n=40)	43
	"Uncertain" neuropathic pain classification	Acute and sub-acute sciatica (n=40)	28
	"Possible" neuropathic pain component	Chronic sciatica (n=26)	46

Study	Numerator	Denominator (N)	Prevalence of neuropathic pain (%)*
	"Uncertain" neuropathic pain classification	Chronic sciatica (n=26)	27
Beith et al. (2011)	"Possible" neuropathic pain component	LBLP (n=227)	23
	"Uncertain" neuropathic pain classification	LBLP (n=227)	27
Japanese neuropathic screening questionnaire			
Orita et al. (2016)	Highly likely, or likely to have a neuropathic pain component (score ≥4)	LBLP (n=1804)	78

Abbreviations: DN4, Doleur Neuropathique en 4 (Bouhassira et al. 2005). Japanese neuropathic screening questionnaire (Ogawa 2010). LANSS, Leeds Assessment of Neuropathic Symptoms and Signs (Bennett 2001). LBLP, Low back-related leg pain. PainDETECT (Freynhagen et al. 2006a). QTSFD, Quebec task force classification of spinal disorder. S-LANSS, Self-report version of the Leeds Assessment of Neuropathic Symptoms and Signs (Bennett et al., 2005).

* The denominator is total number (N) of LBLP in the sample.

† QTSFD, classified as group 2 to 4: Group 2, pain in the lumbar area with proximal radiation (i.e., to lower limb, but not beyond the knee). Group 3, pain in the lumbar area radiating below the knee and no neurological signs. Group 4, pain in the lumbar area radiating towards the foot in a dermatomal distribution, associated with sensory deficits or other neurological signs.

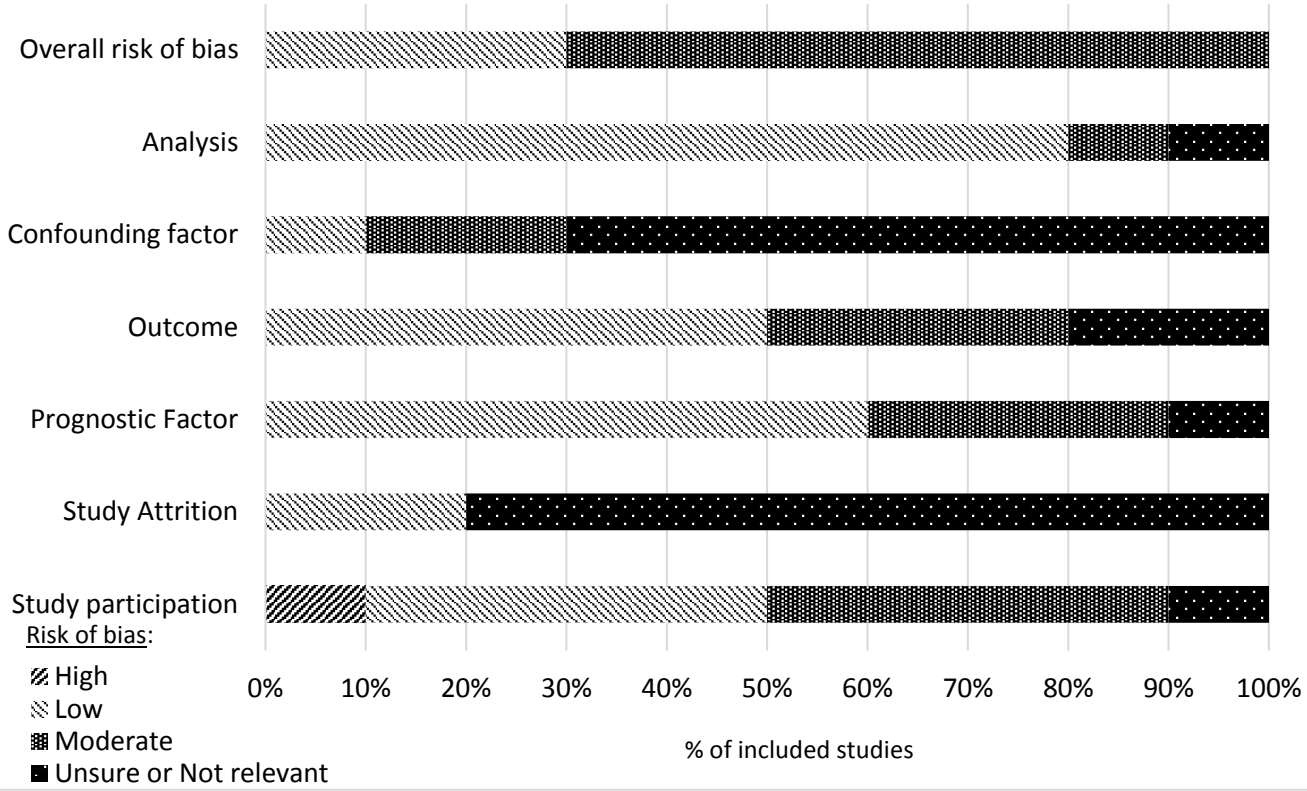
3.4.3 Characteristics

3.4.3.1 Quality assessment of studies describing characteristics and prognosis

Twelve of the included studies underwent quality assessment using the QUIPs tool, by two independent reviewers. A third independent reviewer was necessary to determine the risk of bias of three domains in two of the studies where agreement could not be reached by the two reviewers. Table 3.6 summarises the risk of bias for each of the domains of the QUIPS tool (Hayden et al. 2013) (see Appendix A4 for the full results of the quality assessment process for studies reporting characteristics and prognosis).

Four of the included studies were considered by two independent reviewers to be of low risk of bias (Gierthmühlen et al. 2017, Mahn et al. 2011, Schafer et al. 2011, Walsh and Hall 2009) and eight studies were considered to be of moderate risk of bias (Beith

Table 3.6. Summary of quality assessment (described as risk of bias) of the eleven included studies used to describe characteristics and prognosis



et al. 2011, Defrin et al. 2014, Freynhagen et al. 2008, Hüllemann et al. 2017, Morsø et al. 2011, Smart et al. 2011, Tutoglu et al. 2015, Uher and Bob 2013).

3.4.3.2 Characteristics of neuropathic pain in included studies

Eleven studies described characteristics of neuropathic pain in LBLP, of which eight studies compared LBLP patients with neuropathic pain to LBLP patients with non-neuropathic pain (Beith et al. 2011, Freynhagen et al. 2008, Morsø et al. 2011, Smart et al. 2011, Tutoglu et al. 2015, Uher and Bob 2013, Schafer et al. 2011, Walsh and Hall 2009) or LBP patients with or without leg pain (Gierthmühlen et al. 2017). The characteristics of neuropathic pain in LBLP are summarised in Table 3.7 and described in more detail in the following section, in terms of pain characteristics (for example pain location in the leg), clinical examination findings, LBLP-related disability, psychological characteristics, health related quality of life and medication use.

3.4.3.2.1 Pain characteristics

3.4.3.2.1.1 Pain intensity

Six of the included studies described the association of pain intensity and neuropathic pain in LBLP (Freynhagen et al. 2008, Schafer et al. 2011, Smart et al. 2012a, Walsh and Hall 2009, Gierthmühlen et al. 2017). Visual analogue scales or numerical rating scales were used to determine pain intensity in all of the studies. Pain intensity was reported to be more severe in LBLP patients with neuropathic pain in all but two studies (Freynhagen et al. 2008, Walsh and Hall 2009). Only one study provided information on pain intensity in both the leg and the back (Morsø et al. 2011).

3.4.3.2.1.2 Pain duration and pain location

Four of the included studies reported on pain duration (Defrin et al. 2014, Schafer et al. 2011, Smart et al. 2012a, Gierthmühlen et al. 2017) and four reported on pain

location (Beith et al. 2011, Schafer et al. 2011, Smart et al. 2012a, Freynhagen et al. 2008). Both duration and location will be described in turn below. Two studies reported pain duration in LBLP patients with neuropathic pain in comparison to those without (Gierthmühlen et al. 2017, Schafer et al. 2011), neither study reported any difference between the two groups. The majority of patients in each of the four studies reported pain duration for at least three months, and in many instances pain duration was over one-year, but it is not clear whether this is as a result of sampling methods or whether it is a feature of neuropathic pain. With respect to pain location, from the results of the four studies included in this review, it is likely that LBLP patients with neuropathic pain present with pain below the knee, but it is also likely that LBLP patients with non-neuropathic pain may also present with pain below the knee. Although the location of pain in the leg appears to be a sensitive indicator of neuropathic pain, it does not seem that pain below the knee is a specific indicator of neuropathic pain in LBLP patients.

3.4.3.2.2 LBLP-related disability

Four studies compared LBLP-related disability (Morsø et al. 2011, Schafer et al. 2011, Walsh and Hall 2009, Gierthmühlen et al. 2017) between patients with components of neuropathic pain and those without. Two of the studies (Schafer et al. 2011, Smart et al. 2011) used the LBP specific Roland-Morris Disability Questionnaire (RMDQ) (Roland and Morris 1983), one study (Walsh and Hall 2009) used the Oswestry Disability Index (ODI) (Fairbank et al. 1980) and one used the Hannover Functional Ability Questionnaire (FFbH-R) (Kohlmann and Raspe 1994). In all but one study

(Gierthmühlen et al. 2017), LBLP participants with neuropathic pain reported significantly higher levels of disability compared to participants with non-neuropathic pain. In one of the studies, the difference between groups was also clinically important difference (Morsø et al., 2011). In the study by Gierthmühlen et al. (2017) a similar proportion of patients with and without neuropathic pain had LBLP-related disability but this may be a function of the small sample size (n=51).

3.4.3.2.3 Psychological variables

3.4.3.2.3.1 Depression

Seven studies reported on depression in neuropathic LBLP, using several different measurement tools. Four of the included studies used the depression subscale of the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith 1983) (Schafer et al. 2011, Smart et al. 2012a, Walsh and Hall 2009, Gierthmühlen et al. 2017), two studies used the Beck Depression Inventory (Beck 1970) (Tutoglu et al. 2015, Uher and Bob 2013), the remaining study (Mahn et al. 2011) used the Patient Health Questionnaire (Lowe et al. 2004). Moderate to severe depression was reported in 42% of LBLP patients with neuropathic pain (Mahn et al. 2011). Neuropathic LBLP was associated with more severe depression compared to non-neuropathic LBLP in studies where neuropathic pain was defined using a case ascertainment tool (Tutoglu et al. 2015, Uher and Bob 2013). Whether LBLP patients with neuropathic pain had more severe depression was not conclusive across all studies, in three studies with low risk of bias, Walsh and Hall (2009), Schafer et al (2011) and Gierthmühlen et al (2017) reported no differences in depression severity in LBLP patients with and without neuropathic pain, all three studies defined neuropathic pain based on clinical

examination. Evidence on depression in patients with neuropathic pain compared to those without is inconsistent amongst the studies included in this systematic review.

3.4.3.2.3.2 Anxiety

Anxiety levels were reported by six of the included studies. HADS was used to record anxiety by four of the five included studies (Schafer et al. 2011, Smart et al. 2012a, Walsh and Hall 2009, Gierthmühlen et al. 2017), the Beck anxiety inventory (Beck et al. 1988) was used by one study (Tutoglu et al. 2015) and the Zung self-rating anxiety scale (Zung 1971) was used by Uher et al., (2013). Three of the studies were of low risk of bias (Gierthmühlen et al. 2017, Schafer et al. 2011, Walsh and Hall 2009). Three of the studies reported more severe anxiety in LBLP patients with neuropathic pain compared to non-neuropathic pain (Schafer et al. 2011, Tutoglu et al. 2015, Uher and Bob 2013) and two studies found no difference in anxiety levels between LBLP with and without neuropathic pain (Walsh and Hall 2009, Gierthmühlen et al. 2017). Despite Schafer et al (2011) reporting that LBLP patients with neuropathic pain had more severe anxiety compared to patients without neuropathic pain, the clinical levels of anxiety in the whole cohort was low, and patients with neuropathic pain reported only mild levels of anxiety. Normal to mild levels of anxiety were also found in the cohorts reported by Walsh and Hall (2009) and Smart et al., (2011), in the study by Gierthmühlen et al (2017) a third of patients (4 out of 12) with neuropathic pain were considered to have possible anxiety. From studies with low risk of bias, there is inconsistent evidence that patients with neuropathic pain report higher levels of anxiety compared to those without and this in part, may be due to small samples.

3.4.3.2.3.3 Fear avoidance

Fear avoidance measured using the Fear avoidance beliefs questionnaire (FABQ) (Waddell et al. 1993) was reported by two of the included studies (Schafer et al. 2011, Walsh and Hall 2009). Neither study reported any significant differences in the work subscale of the FABQ, but Walsh and Hall (2009) reported significant differences in the physical activity subscale between LBLP groups with and without neuropathic pain.

3.4.3.2.3.4 Sense of coherence, suppression and alexithymia

Sense of coherence (Antonovsky 1993), alexithymia (Parker et al. 2003) and suppression (Hasenbring et al. 1994) were psychological characteristics reported in addition to depression, anxiety and fear avoidance for LBLP patients with neuropathic pain, using validated scales. Morsø et al. (2011) reported that LBLP patients had significantly lower sense of coherence (a high sense of coherence assists a patient with coping) if they presented with underlying neuropathic pain compared to patients with non-neuropathic pain. The same study also reported those patients with LBLP and neuropathic pain are more likely to be depressed suppressors compared to those without neuropathic pain. Suppression is a cognitive coping strategy whereby the patient suppresses the perception of pain in order to continue with daily activities, but suppression itself leads to emotional distress. Alexithymia, which describes one's trouble understanding and communicating how one feels, was associated with more severe symptoms in LBLP patients with neuropathic pain, compared to LBLP patients with both ambiguous pain and non-neuropathic pain (Uher and Bob 2013). Overall, it is difficult to make any clear conclusions whether these psychological characteristics are

features of neuropathic pain, or that they might be due to the differences in the samples used in the studies.

3.4.3.2.4 Health related quality of life

Four of the included studies reported on aspects of quality of life and general health, including sleep. Findings on health related quality of life and sleep will be described in turn below. The short form (SF-36) health survey (Ware 2000) and the shorter version (SF-12) health survey were used to report on quality of life by two studies (Tutoglu et al. 2015, Gierthmühlen et al. 2017). Morsø et al (2011) used a numerical rating scale (0-10) for participants to self-report general health. Two out of the three studies, both with moderate risk of bias, reported that general health in LBLP patients with neuropathic pain was worse than those with non-neuropathic pain (Morsø et al. 2011, Tutoglu et al. 2015). Two studies (Mahn et al. 2011, Gierthmühlen et al. 2017) reported on sleep using the Medical Outcome Study sleep scale (Hays et al. 2005). The study by Mahn et al (2011) reported that sleep was optimal in 37.1% of LBLP patients with neuropathic pain and patients with neuropathic pain commonly reported sleep disturbance and somnolence. It is not clear whether sleep is any more disturbed in LBLP with neuropathic pain compared to those patients without neuropathic pain.

3.4.3.2.5 Neurological examination

Two of the included studies (Freynhagen et al., 2008, Defrin et al., 2014) used quantitative sensory testing (QST) to determine the presence or absence of any sensory signs associated with neuropathic pain. One study reported the presence of sensory symptoms (burning pain, prickling pain, allodynia, numbness, pain attacks,

light pressure pain and spontaneous pain) derived from self- in patients defined as having neuropathic pain based on clinical examination report (Gierthmühlen et al. 2017). Freynhagen et al., (2008) also reported the clinical characteristics of patients clinically diagnosed with either radicular (which they considered synonymous to neuropathic pain) or pseudoradicular pain.

When using QST as an extension of normal neurological examination, LBLP patients clinically assessed to have non-neuropathic pain were as likely to have sensory changes as LBLP patients who were clinically assessed to have neuropathic pain (Freynhagen et al. 2008). Characteristics of neurological examination based on the study by Freynhagen et al. (2008) suggest that it is likely that more patients with neuropathic pain have sensory deficits and changes in straight leg raise, but that the presence of sensory symptoms may not be a specific indicator of neuropathic pain (Gierthmühlen et al. 2017, Freynhagen et al. 2008).

The study by Defrin et al (2014), based on findings from QST, reported that the majority of LBLP patients with neuropathic pain were found to have allodynia on the symptomatic leg but the presence of allodynia did not significantly affect the intensity of self-reported leg pain (base on a numerical rating scale (NRS)). The findings of the study by Defrin et al., (2014) are without comparison to a non-neuropathic group but as with the findings by Freynhagen et al., (2008) they provide a description of findings from the clinical examination of LBLP patients with neuropathic pain.

3.4.3.2.6 Pain medications

Three of the included studies reported on medication use of LBLP patients with neuropathic pain. Two out of three studies, both at moderate risk of bias, reported that patients with neuropathic pain more commonly used pain medications compared to those without (Morsø et al. 2011, Freynhagen et al. 2008) and there was some evidence that patients with neuropathic pain used stronger pain medications more often (Freynhagen et al. 2008). In one study at low risk of bias, there was no difference in the current pain medications used by patients with and without neuropathic pain (Gierthmühlen et al. 2017). There was inconsistent evidence of pain medication use by patients with neuropathic pain compared to those without and it is not clear from these studies whether medication use is a feature of neuropathic pain or as a result of the sampling methods used.

Table 3.7 Studies showing characteristics of neuropathic pain

Characteristic associated with neuropathic pain	Study	Outcome measure used	LBLP patients with neuropathic pain	LBLP with non-neuropathic pain	Reported P
Pain intensity	(Freynhagen et al. 2008)	NRS 0 to 10 (unspecified whether for back or leg)	Mean 6.4 (SD 1.8)	Mean 5.3 (SD 2.3)	0.19
	(Morsø et al. 2011)	NRS 0 to 10 leg pain	Leg pain median 8.0, IQR 5.3 to 8.0	Leg pain median 4.0, IQR 1.0 to 6.0	0.012
		NRS 0 to 10 back pain	Back pain median 7.0, IQR 5.0 to 8.8	Back pain median 6.0, IQR 4.0 to 7.0	0.000
	(Schafer et al. 2011)	NRS 0 to 10 (unspecified whether back or leg)	Neuropathic sensitisation mean 5.8 (SD 1.7); peripheral nerve sensitisation mean 5.3 (SD	Mean 4.6 (SD 1.4)	0.031

Characteristic associated with neuropathic pain	Study	Outcome measure used	LBLP patients with neuropathic pain	LBLP with non-neuropathic pain	Reported P
			1.7); denervation mean 4.6 (SD 1.5)		
	(Tutoglu et al. 2015)	VAS 0 to 10 (unspecified whether back or leg)	Mean 8.0 (SD 1.6)	Mean 6.6 (SD 3.4)	0.033
	(Walsh and Hall 2009)	VAS 0 to 10 (unspecified whether back or leg)	Neuropathic sensitisation mean 6 (SD 3); peripheral nerve sensitisation mean 7 (SD 2); denervation mean 6 (SD 3)	Mean 5 (SD 3)	0.23
	(Gierthmühlen et al. 2017)	NRS 0 to 10 (unspecified whether for back or leg)	Mean 5.6 (SD 1.5)	Mean 4.0 (2.5)	<0.05

Characteristic associated with neuropathic pain	Study	Outcome measure used	LBLP patients with neuropathic pain	LBLP with non-neuropathic pain	Reported P
Pain location	(Beith et al. 2011)	% reporting pain below the knee	79% of LBLP patients with possible neuropathic pain, 74% of LBLP with uncertain pain	57%	n/a
	(Freynhagen et al. 2008)	% reporting pain in the leg	Radiating pain below the knee: in S1 dermatomal distribution 25%, in L5 dermatomal distribution 50%, to L4 17%, to L4 & L5 8%	Radiating pain to the gluteal region or thigh (but not below knee) 100%	n/a
	(Schafer et al. 2011)	% reporting pain below knee	Neuropathic sensitisation 80.0%, peripheral nerve sensitisation 88.9%, denervation 71.4%	73.7%	0.71

Characteristic associated with neuropathic pain	Study	Outcome measure used	LBLP patients with neuropathic pain	LBLP with non-neuropathic pain	Reported P
	(Smart et al. 2012a)	Predominant pain location	Back 9%, back/thigh 19%, unilateral leg pain below knee 59%, back and unilateral leg pain below knee 11%, bilateral leg pain below knee 1%	n/a	n/a
Pain duration	(Defrin et al. 2014) *	Years	With allodynia mean 5.7 (SD 5.6) Without allodynia mean 2.7 (SD 2.9)	n/a	n/a
	(Schafer et al. 2011)	Current episode (months)	Neuropathic sensitisation mean 7.0 (SD 18.4); peripheral nerve sensitisation mean 6.0 (SD	Mean 10.6 (SD 12.2)	0.76

Characteristic associated with neuropathic pain	Study	Outcome measure used	LBLP patients with neuropathic pain	LBLP with non-neuropathic pain	Reported P
			12.5); denervation mean 7.3 (SD 11.3)		
	(Smart et al. 2012a)	Current episode	0 to 12 weeks (34%), 4 to 12 months (43%), 1 year and over (23%)	n/a	n/a
	(Gierthmühlen et al. 2017)		Unknown n=7 (13.7%)	Unknown n=0 (0%)	ns
			¼ to 1 year n=9 (17.5%)	¼ to 1 year n=7 (21.9%)	
			>1 to 2 years n=3 (5.9%)	>1 to 2 years n=2 (6.3%)	
			>5 to 10 years n=4 (21.1%)	>5 to 10 years n=7 (21.9%)	
			More than 10 years n=17 (33.3%)	More than 10 years n=14 (43.8%)	

Characteristic associated with neuropathic pain	Study	Outcome measure used	LBLP patients with neuropathic pain	LBLP with non-neuropathic pain	Reported P
LBLP-related disability	(Morsø et al. 2011)	RMDQ (0 to 23 NRS)	Median 18, IQR 14 to 20	Median 10, IQR 7 to 15	0.000
	(Schafer et al. 2011)	RMDQ (0 to 24 NRS)	Neuropathic sensitisation mean 10.5 (SD 4.0); peripheral nerve sensitisation mean 5.3 (SD 1.7); denervation mean 8.7 (SD 4.5)	Mean 6.5 (SD 3.3)	0.014
	(Gierthmühlen et al., 2017)	FFbH-R	Normal (80-100%): n=2 (16.7%) Moderate (60-79%): n=6 (50.0%)	Normal (80-100%): n=11 (35.5%) Moderate (60-79%): n=9 (29.0%)	ns

Characteristic associated with neuropathic pain	Study	Outcome measure used	LBLP patients with neuropathic pain	LBLP with non-neuropathic pain	Reported P
			Relevant impairment (< 60%): 4 (33.4%)	Relevant impairment (< 60%): 11 (35.5%)	
	(Walsh and Hall 2009)	ODI[†]	Neuropathic sensitisation mean 37 (SD 5); peripheral nerve sensitisation mean 52 (SD 17); denervation mean 32 (SD 10)	Mean 30 (SD 10)	0.001
Psychological characteristics (depression)	(Mahn et al. 2011)[*]	PH9	None (23%), mild (35%), moderate (37%), severe (5%).	n/a	n/a
	(Schafer et al. 2011)	HADS[§]	Neuropathic sensitisation mean 9.1 (SD 4.6); peripheral nerve sensitisation mean 4.9 (SD	Mean 7.2 (SD 4.0)	0.37

Characteristic associated with neuropathic pain	Study	Outcome measure used	LBLP patients with neuropathic pain	LBLP with non-neuropathic pain	Reported P
			2.5); denervation mean 5.6 (SD 3.6)		
	(Smart et al. 2012a)	HADS[§]	Mean 7.0 (SD 4.4)	n/a	n/a
	(Tutoglu et al. 2015)	BDI[‡]	Mean 20.9 (SD 12.4)	Mean 5.9 (SD 5.4)	<0.001
	(Uher and Bob 2013)	BDI-II[‡]	Neuropathic pain group mean 14.4 (SD 9.2); ambiguous pain mean 12.9 (SD 7.6)	Mean 9.3 (SD 5.0)	<0.01
	(Walsh and Hall 2009)	HADS[§]	Neuropathic sensitisation mean 7 (SD 4); peripheral nerve sensitisation mean 8	Mean 5 (SD 3)	0.12

Characteristic associated with neuropathic pain	Study	Outcome measure used	LBLP patients with neuropathic pain	LBLP with non-neuropathic pain	Reported P
			(SD 4); denervation mean 5 (SD 3)		
	(Gierthmühlen et al., 2017)	HADS§	Mean 5.0 (SD 4.5)	Mean 6.3 (SD 4.0)	ns
			Score ≥ 8: n=2 (16.7%)	Score ≥ 8: n=10 (33.3%)	ns
Psychological characteristics (anxiety)	(Schafer et al. 2011)	HADS§	Neuropathic sensitisation mean 9.1 (SD 4.6); peripheral nerve sensitisation mean 4.9 (SD 2.5); denervation mean 5.6 (SD 3.6)	Mean 7.2 (SD 4.0)	0.013
	(Smart et al. 2012a)	HADS§	Mean 7.5 (SD 4.4)	n/a	n/a

Characteristic associated with neuropathic pain	Study	Outcome measure used	LBLP patients with neuropathic pain	LBLP with non-neuropathic pain	Reported P
	(Tutoglu et al. 2015)	BAI‡	Mean 10.2 (SD 10.8)	Mean 3.1 (SD 3.7)	<0.001
	(Uher and Bob 2013)	SAS‖	Neuropathic pain mean 42.9 (SD 8.5); ambiguous pain mean 39.2 (SD 7.3)	Mean 35.8 (SD 8.5)	<0.01
	(Walsh and Hall 2009)	HADS§	Neuropathic sensitisation mean 9 (SD 4); peripheral nerve sensitisation mean 10 (4); denervation mean 7 (SD 3)	Mean 7 (SD 2)	0.14
	(Gierthmühlen et al., 2017)	HADS§	Mean 5.7 (SD 4.9)	Mean 7.0 (SD 4.2)	ns
			Score ≥ 8: n=4 (33.3%)	Score ≥ 8: n=15 (50.0%)	ns

Characteristic associated with neuropathic pain	Study	Outcome measure used	LBLP patients with neuropathic pain	LBLP with non-neuropathic pain	Reported P
Psychological characteristics (fear avoidance)	(Schafer et al. 2011)	FABQ**	Neuropathic sensitisation mean 39.1 (SD 19.1); peripheral nerve sensitisation mean 36.4 (SD 18.8); denervation mean 34.3 (SD 19.0)	Mean 29.8 (SD 21.2)	0.51
	(Walsh and Hall 2009)	FABQ** - Physical activity	Neuropathic sensitisation mean 16 (SD 3); peripheral nerve sensitisation mean 20 (SD 4); denervation mean 12 (SD 5)	Mean 18 (SD 3)	0.001
	(Walsh and Hall 2009)	FABQ** - Work	Neuropathic sensitisation mean 22 (SD 11); peripheral nerve sensitisation mean 21	Mean 22 (SD 13)	0.99

Characteristic associated with neuropathic pain	Study	Outcome measure used	LBLP patients with neuropathic pain	LBLP with non-neuropathic pain	Reported P
			(SD 11); denervation mean 21 (SD 13)		
Health related quality of life	(Morsø et al. 2011)	Self-rated general health (0-10)	Median 2, IQR 1 to 3	Median 3, IQR 2 to 4	0.001
	(Tutoglu et al. 2015)	SF-36[††] physical function (NRS 0 to 100)	Mean 44.3 (SD 26.3)	Mean 77.7 (SD 24.7)	<0.001
		SF-36[††] physical role	Mean 31.9 (SD 40.8)	Mean 56.8 (SD 43.2)	<0.001
		SF-36[††] emotional role	Mean 35.2 (SD 42.9)	Mean 64.0 (SD 42.6)	<0.001
		SF-36[††] social function	Mean 36.7 (SD 42.9)	Mean 53.7 (SD 18.1)	<0.001
		SF-36[††] mental health	Mean 47.2 (SD 13.5)	Mean 55.1 (SD 11.6)	<0.001
		SF-36[††] energy/vitality	Mean 36.8 (SD 19.1)	Mean 51.1 (SD 13.4)	<0.001
		SF-36[††] pain	Mean 37.3 (SD 18.9)	Mean 55.0 (SD 22.8)	<0.001

Characteristic associated with neuropathic pain	Study	Outcome measure used	LBLP patients with neuropathic pain	LBLP with non-neuropathic pain	Reported P
		SF-36[††] general health	Mean 36.1 (SD 13.3)	Mean 40.8 (SD 10.9)	<0.001
	(Gierthmühlen et al., 2017)	State of health (NRS 0 to 100)	Mean 63.8 (SD 22.5)	Mean 59.5 (SD 18.9)	ns
		SF-12[††] mental health	Mean 53.3 (SD 11.5)	Mean 45.9 (SD 12.4)	ns
		SF-12[††] physical health	Mean 34.9 (SD 8.2)	Mean 38.8 (SD 8.7)	ns
Health related quality of life (sleep)	(Mahn et al. 2011) [*]	MOS sleep scale [††]	Disturbance mean 45 (SD 25), somnolence mean 40 (SD 22), sleep adequacy mean 51 (SD 28). Optimal sleep 37%	n/a	n/a
	(Gierthmühlen et al., 2017)	MOS sleep scale [††]	Disturbance mean 42.4 (SD 20.6), somnolence mean 43.1 (SD 20.5), sleep	Disturbance mean 40.1 (SD 21.8), somnolence mean 41.5 (SD 21.9), sleep	ns

Characteristic associated with neuropathic pain	Study	Outcome measure used	LBLP patients with neuropathic pain	LBLP with non-neuropathic pain	Reported P
			adequacy mean 61.4 (SD 22.5)	adequacy mean 62.6 (SD 22.5)	
Items from neurological examination	(Freynhagen et al. 2008)	Clinical examination	Positive neural tension tests (proportion of sample, 42%), positive straight leg raise (50%), reflex deficit (25%), sensory deficit (58%), motor deficit (25%)	Positive straight leg raise (proportion of sample, 13%), sensory deficit (20%)	n/a
Pain descriptors	(Mahn et al. 2011) *	Self-reported neuropathic characteristics	Burning (25%), prickling (26%), allodynia (10%), attacks (32%), thermal induced pain (8%), numbness (16%), pressure induced pain (21%)	n/a	n/a

Characteristic associated with neuropathic pain	Study	Outcome measure used	LBLP patients with neuropathic pain	LBLP with non-neuropathic pain	Reported P
	(Gierthmühlen et al., 2017)	Burning pain	Back, n=7 (36.8%), leg, n=10 (52.6%)	n=3 (9.4%)	<0.05
		Prickling pain	Back n=11 (57.9%), leg, n=15 (78.9%)	n=7 (21.9%)	<0.01
		Self-reported allodynia	Back, n=7 (36.8%), leg, n=3 (15.8%)	n=2 (6.3%)	<0.01
		Self-reported numbness	Back, n=13 (68.4%), leg, n=13 (68.4%)	n=3 (9.4%)	<0.05
		Pain attacks	Back, n=10 (52.6%), leg, n=8 (42.1%)	n=17 (53.1%)	ns
		Light pressure pain	Back, n=12 (63.2%), leg, n=8 (31.6%)	n=14 (43.8%)	ns

Characteristic associated with neuropathic pain	Study	Outcome measure used	LBLP patients with neuropathic pain	LBLP with non-neuropathic pain	Reported P
		Spontaneous pain	Back, n=13 (68.4%), leg, n=11 (57.9%)	n=9 (28.1%)	<0.01
Pain medication	(Gierthmühlen et al., 2017)	Current pain medication	NSAID n=24 (47.1%)	NSAID n=17 (53.1%)	ns
			Weak opioids n=0 (0%)	Weak opioids n=0 (0%)	
			Antidepressants and/or anticonvulsants n=1 (2%)	Antidepressants and/or anticonvulsants n=1 (3.1%)	
			None n=15 (29.4%)	None n=11 (34.4%)	
	(Freynhagen et al. 2008)	Current pain medication	NSAID or Cox-2 n=6 (50%)	NSAID or Cox-2 n=8 (53.3%)	n/a
			Weak or strong opioids n=10 (83.3%)	Weak or strong Opioids n=2 (13.3%)	
			Antidepressants and/or anticonvulsants n=5 (41.7%)	Antidepressants and/or anticonvulsants n=1 (6.7%)	

Characteristic associated with neuropathic pain	Study	Outcome measure used	LBLP patients with neuropathic pain	LBLP with non-neuropathic pain	Reported P
			Skeletal muscle relaxant n=0 (0%) None n=0 (0%)	Skeletal muscle relaxant n=2 (13.3%) None n=6 (40%)	
	(Morsø et al. 2011)	Taking pain medication	n=21 (75%)	n=40 (52%)	0.025

Abbreviations: BAI, Beck anxiety inventory. BDI, Beck depression inventory. BDI-II, Beck depression inventory (Czech version). Cox-2, Cox-2 inhibitor FABQ, Fear avoidance beliefs questionnaire. FFbH-R, Hannover Functional Ability Questionnaire. IQR, interquartile range. LBLP, low back-related leg pain. MOS, Medical outcome study. n/a, not applicable. Ns, non-significant. NRS, numerical rating scale. NSAID, non-steroidal anti-inflammatory drug. ODI, Oswestry Disability Index. PH9, patient health questionnaire. RMDQ, Roland Morris Disability Questionnaire. SAS, Zung self-rating anxiety scale (Czech version). SD, standard deviation. SF-36, the Short Form (36) Health Survey. TAS-20, Toronto alexithymia scale (Czech version) where alexithymia is defined as being functionally unaware of your emotions. VAS, visual analogue scale.

* Characteristics derived from case control studies and the reported associations are for LBLP patients with neuropathic pain only.

† ODI is a 10 item scale using a 0 to 5 Likert scale, and is reported as a %.

‡ BAI, BDI and BDI-II consist of 21 items, using a 0 to 3 Likhert scale with a maximum possible score of 63.

§ HADS consists of two (one for anxiety, one for depression) scales with 7 items, using 0 to 3 Likhert scale, with a maximum possible score of 21 on each scale.

|| SAS consists of 20 items, using 1 to 4 Likhert scale, the score ranges from 20 to 80.

** FABQ is comprised of a physical activity component (total score of 24, 4 items) and a work component (total score of 42, 7 items).

†† Each item of SF-12, SF-36 and the MOS Sleep scale is scored on a 0 to 100 scale, higher scores indicate greater disability.

3.4.4 Prognosis

Three studies reported longitudinal data (Morsø et al. 2011, Schafer et al. 2011, Hüllemann et al. 2017), one of which described overall prognosis (clinical course) (Morsø et al. 2011) and one described the change in the presence of neuropathic pain over time (Hüllemann et al. 2017). None of the three studies provided any evidence of prognostic factors of neuropathic pain in LBLP. Each of the studies are described in turn below.

Schafer et al. (2011) reported on patient outcomes following treatment, patients were clinically assessed to have neuropathic LBLP, both with and without neuropathic characteristics (patients were classified into one of three neuropathic pain groups, neuropathic sensitisation, denervation, peripheral nerve sensitisation and one non-neuropathic pain group, musculoskeletal). They reported that the greatest improvement in outcomes was in LBLP patients with peripheral nerve sensitisation, and the least improvement in LBLP patients with neuropathic sensitisation. A number of potential limitations were acknowledged by the authors (Schafer et al. 2011): short follow-up time (mean duration of treatment varied from 25 days to 33 days), lack of control group, and a large proportion of ineligible patients.

Morsø et al. (2011) followed up LBLP patients at three and twelve months (outcomes were back and leg pain intensity, leg and back-related disability and self-reported general health) and showed that for both patient groups (with neuropathic and without neuropathic pain) most outcomes improved over time (see Table 3.8 for a summary of the study by Morsø et al. (2011)). At three and twelve months, LBLP

patients with neuropathic pain remained worse compared to those with non-neuropathic pain in all outcomes except back pain intensity.

Hüllemann et al. (2017) followed up LBLP patients with pain duration less than three months at baseline, who re-attended three to twelve months after their initial visit. Patients with pain duration at baseline greater than three months who re-attended on two occasions (three to twelve months and twelve to 24-months) after their initial visit were also followed up. In patients who re-attended and had complete observations at each time point, mean neuropathic pain (based on PainDETECT) was reported and did not change over time (see Table 3.9 for a summary of this study). The domains relating to confounding and attrition for the study by Hüllemann et al (2017) were assessed to be at high risk of bias (see Appendix A4) (the overall risk of bias was moderate) because very few patients were followed up and it is likely that patients who re-attended were different to those who did not, further research is likely to change the estimate provided by this study.

Table 3.8 Study by Morsø et al. (2011) showing overall prognosis[*] of neuropathic pain in low back-related leg pain (n=145)

Outcome	**LBLP patients with neuropathic pain[*]**					**LBLP patients with non-neuropathic pain[*]**					**Difference in median values between patients with and without neuropathic pain[§]**		
	Base-line	3 months		12 months		Base-line	3 months		12 months		Base-line	3 months	12 months
	Med	Med	P	Med	P	Med	Med	P	Med	P	P	P	P
Back pain intensity (NRS 0-10)	7.0	5.2	0.011	4.3	0.001	6.0	4.0	0.002	4.8	0.003	0.012	0.054	0.214
Leg pain intensity (NRS 0-10)	8.0	6.0	0.007	4.0	0.002	4.0	2.3	0.023	1.7	0.032	>0.001	0.001	0.022
LBLP-related disability (RMDQ 0-23)	17.5	14.0	0.016	13.5	0.008	10.0	9.0	0.001	5.0	>0.001	>0.001	>0.001	0.009

Outcome	LBLP patients with neuropathic pain*					LBLP patients with non-neuropathic pain*					Difference in median values between patients with and without neuropathic pain§		
	Base-line	3 months		12 months		Base-line	3 months		12 months		Base-line	3 months	12 months
	Med	Med	P	Med	P	Med	Med	P	Med	P	P	P	P
Self-reported general health†	2.0	3.0	0.072	3.0	0.012	3.0	4.0	>0.001	4.0	0.004	0.001	0.010	0.033

Abbreviations: Med, Median value, NRS, numerical rating scale. RMDQ, Roland Morris Disability Questionnaire. * using results obtained through personal communication with the author †PainDETECT was used to ascertain neuropathic pain status ‡ Self-reported general health was rated on a 7 point Likert scale where "unbearable" was scored as 0 and "excellent" as 7. § Differences in median values are shown as reported P value

Table 3.9 Study by Hüllemann et al. (2017) showing change in the presence of neuropathic pain in low back-related leg pain

	PainDETECT* scores at baseline					
	Baseline		Follow-up at 3 to 12 months		Follow-up at 12 to 24 months	
	n	Mean (SD)	Mean (SD)	P	Mean (SD)	P
Patients with pain duration < 3 months†						
Pain radiating to above knee (group 2)	86	11.3 (6.4)	11.1 (6.4)	0.85	-	-
Pain radiating to below knee (but not the foot) (group 3)	48	13.3 (6.7)	13.5 (6.7)	0.90	-	-
Pain radiating to at least one foot (group 4)	19	14.1 (7.8)	10.6 (7.8)	0.08	-	-
Patients with pain duration > 3 months‡						
Pain radiating to above knee (group 2)	267	13.4 (6.7)	13.6 (6.8)	0.61	13.7 (6.3)	0.51
Pain radiating to below knee (but not the foot) (group 3)	173	14.9 (6.2)	15.4 (6.3)	0.27	14.7 (6.6)	0.70
Pain radiating to at least one foot (group 4)	51	15.0 (7.4)	16.0 (5.8)	0.20	14.8 (6.3)	0.79

Abbreviations: n, count. SD, standard deviation of mean. * PainDETECT was used to ascertain neuropathic pain status, a score of ≤ 12 indicates a neuropathic component is likely, a score of 13 to 18 indicates a neuropathic component may be present and a score ≥ 19 indicates a neuropathic component is likely. †Patients with complete data for baseline and at the 1st follow-up were analysed. ‡Patients with pain who had complete data for baseline and 2 follow-up visits were analysed.

3.5 Discussion

This is the first systematic review to look at the prevalence, characteristics and prognosis of neuropathic pain in LBLP. Heterogeneity of the included studies prevented meta-analysis, but comparisons between studies and settings were still possible in relation to study quality, strengths and weaknesses and study design.

3.5.1 Prevalence

In this systematic review, prevalence estimates were extrapolated from data from ten studies that were based in either primary care or in clinical settings that patients could feasibly have accessed directly as first contact care, and therefore the population samples were considered to be similar. Overall prevalence estimates reported in this systematic review varied widely (5% to 80%). There was some consistency for the prevalence of "possible" neuropathic LBLP, based on PainDETECT, which was reported between 19% and 22%. This is not the first review to report variation in prevalence estimates, variation is reported in reviews of neuropathic pain populations in the general population (irrespective of clinical condition) (van Hecke et al. 2014) and in populations seeking care for non-specific LBP (Hush and Marcuzzi 2012, Fishbain et al. 2014). Variation in the reported neuropathic pain prevalence estimates in this systematic review is likely in part to be a function of the patient sample in each study, as the majority of included studies had small sample sizes and the uncertainty around the prevalence estimate from each study remains unknown as the studies did not report confidence intervals. Another reason for variation is likely to be due to the methods used by each study for defining neuropathic pain cases.

Variation in prevalence due to differences in the case ascertainment tools is reasonable to consider (van Hecke et al. 2014). In a study included in this review, Walsh and Hall (2009) reported prevalence of 33% (15 out of 45 patients) using s-LANSS but in a different study using the same cohort (both studies were conducted at the same time), a prevalence of 42% (19 out of 45 patients) was reported when using the DN4. The later study by Walsh et al. (2012) demonstrates that case ascertainment tools may identify different patients due to subtle differences in the tools' questions and the presence or absence of clinical examination tests within each tool (VanDenKerkhof et al. 2015). Identification of LBLP subgroups on the basis of the presence or absence of neuropathic characteristics is supported by previous research in patients with LBLP and other neuropathic pain conditions such as painful diabetic neuropathy and post-herpetic neuralgia (Baron et al. 2012). The results of this systematic review show that LBLP patients with sciatica show higher prevalence of neuropathic pain than those samples with mixed cases of sciatica and referred leg pain, but not all patients with sciatica have neuropathic pain, whereas some patients have referred leg pain which is neuropathic. These results support the argument for the presence of distinct subgroups of LBLP patients with neuropathic pain. It is important to determine whether those LBLP patients with neuropathic pain present with worse morbidity compared to those without.

3.5.2 Characteristics and prognosis

The included studies in this systematic review reported some consistent evidence for more severe pain intensity in LBLP patients with neuropathic pain. In part, this is

consistent with the literature on the wider group of patients with neuropathic LBP, (Freynhagen et al. 2006b, Kew et al. 2017) but it is not clear whether LBLP patients with neuropathic pain report more severe leg or back pain, or both. Eight of the studies included in this review, albeit at moderate risk of bias, found that LBLP patients with neuropathic pain reported more severe back and leg pain related disability, health related quality of life, pain intensity, depression and anxiety than those without neuropathic pain. The three remaining studies (Schafer et al. 2011, Walsh and Hall 2009, Gierthmühlen et al. 2017), assessed to be of low risk of bias, reported fewer differences in pain duration, LBLP-related disability, depression, anxiety, and health related quality of life between patients with and without neuropathic pain. Unlike the other included studies, these three used clinical assessment to identify cases of neuropathic pain in LBLP patients. In clinical practice, especially in settings such as primary care, the use of case ascertainment tools is rare and neuropathic pain is more commonly defined using clinical history and examination. All three studies, had small samples and it may be argued they lacked the power to detect any differences in characteristics between groups. Gierthmühlen et al. (2017) used a comparator group that may have included LBP patients with or without leg pain, and as LBP patients without leg pain report less pain-related morbidity (Konstantinou et al. 2013), this may have inflated differences between subgroups. Comparison to a wider group of LBP by Gierthmühlen et al. (2017) adds confidence in the finding that LBLP patients with neuropathic pain based on clinical diagnosis present with fewer differences in LBP-related morbidity compared to those cases defined by case ascertainment tools.

Individual components from history taking (pain location) and neurological clinical examination were reported in a number of studies included in this review. In five of the studies (Beith et al. 2011, Freynhagen et al. 2008, Smart et al. 2011, Schafer et al. 2011, Gierthmühlen et al. 2017), pain below the knee was associated with neuropathic pain, but not all patients with neuropathic pain had below knee pain. This finding, that individual components of clinical history and examination (pain location, neurological findings) are not specific indicators of neuropathic pain, is supported by the wider literature on LBP patients with neuropathic pain. Freynhagen et al (2008) and Gierthmühlen et al (2017) reported that patients with non-neuropathic pain have sensory deficits and positive findings on neural tension tests. The finding that neurological signs and deficits might not be exclusive to patients with neuropathic pain is supported by who reported that patients with neuropathic characteristics were more typical of sciatica patients but neuropathic characteristics were not restricted to patients clinically diagnosed with sciatica. Conversely, a subgroup of patients with a clinical diagnosis of sciatica have no features of neuropathic pain (Mahn et al. 2011, Walsh and Hall 2009, Schafer et al. 2011), and patients with referred leg pain may have features of pain that is neuropathic. The underlying mechanism of LBLP is thought to be mixed, where neuropathic and nociceptive mechanisms coexist, but in some circumstances inflammatory mechanisms can produce similar characteristics to neuropathic mechanisms (for example, pain attacks and allodynia). The results of this review suggest that there may be subgroups of LBLP patients with or without neuropathic pain but it is not clear whether these subgroups differ in their future clinical outcomes or in their response to targeted treatments.

Two of the three identified studies with longitudinal data described prognosis in LBLP patients with neuropathic pain (Morsø et al. 2011, Hüllemann et al. 2017). Morsø et al (2011) found that both patients with and without neuropathic characteristics improved over time, but that LBLP patients with neuropathic characteristics improved to a lesser extent in terms of disability, pain and self-reported general health, compared to those without neuropathic pain. Hüllemann et al 2017 reported that the presence of neuropathic pain in LBLP did not change over time in patients who re-attended a pain clinic although confidence in this result is low as it was likely that the patients who attended a follow-up appointment were different to those who did not. Morsø et al (2011) did not report whether LBLP may change from a neuropathic state to non-neuropathic and vice versa, and neither study investigated prognostic factors associated with recovery/non-recovery in terms of pain or disability, in LBLP patients with neuropathic pain.

It is physiologically feasible that underlying nociceptive stimuli causing LBLP, for example degeneration of an intervertebral disc, over time may involve microscopic nerve fibres (Baron et al. 2016). This involvement may lead to secondary lesions of the nerve fibres and give rise to neuropathic signs and symptoms in patients who initially presented with nociceptive pain. Conversely, neuropathic pain is often assumed to persist but there is a lack of empirical evidence to fully understand whether patients who initially present with neuropathic pain continue to have signs and symptoms of neuropathic pain over time. Prognostic research offers the opportunity for clinicians and patients to understand what is likely to happen to pain and other symptoms, in

the future. The apparent absence of prognostic research in LBLP patients with neuropathic pain highlights a gap in the literature warranting future research.

This systematic review shows low levels of agreement on the characteristics of LBLP with neuropathic pain derived from cross-sectional studies, and it highlights a gap in the evidence in the description of these patients in primary care. Cross-sectional studies can provide valid evidence of associations for stable characteristics, such as gender. In the context of this systematic review, depression and anxiety is, in some studies, associated with neuropathic pain in LBLP patients, but depression is also linked to the number of pain locations (Gerrits et al. 2014). It is not clear from this systematic review whether LBLP patients with neuropathic pain have higher levels of depression or anxiety or whether this is a spurious finding confounded by the number of pain locations. One of the key weaknesses of cross-sectional data is that they do not offer any temporal relationship and thus prognosis can only be derived from longitudinal research. Identifying subgroups of LBLP patients with or without neuropathic pain and investigating the prognosis of these patients is important in order to describe and understand the likelihood of different outcomes (Croft et al. 2015).

3.5.3 Strengths and weaknesses

This review used a comprehensive systematic approach that was applied throughout the study. An exhaustive search strategy was developed and six search engines searched, additional searches and citation tracking was also executed, however some supporting evidence may have been missed, for example, studies not published as full text or unpublished student studies. An important strength of this review is the use of

two quality assessment tools, one for prevalence studies and one for the studies on characteristics and prognosis of neuropathic pain in LBLP.

3.5.4 Implications for research and clinical practice

This systematic review highlights the need for high quality research to describe the epidemiology of neuropathic pain in LBLP patients in primary care. There is a clear gap in the evidence of both cross-sectional description of baseline characteristics as well as the prognosis of neuropathic pain in this patient population. It is important to determine whether the prognosis of these different groups of LBLP patients differ over time to inform both clinicians and LBLP patients.

3.6 Conclusions

A comprehensive search of the literature and systematic review was carried out on the epidemiology of neuropathic pain in LBLP in primary care, looking at specific objectives on prevalence, characteristics and prognosis. A number of studies were identified that described prevalence and characteristics, two studies described prognosis. Prevalence of neuropathic LBLP based on PainDETECT was estimated to be between 19 and 22%, otherwise there was a wide variation in prevalence estimates (5% to 80%). There was some evidence of higher levels of morbidity in LBLP patients with neuropathic pain compared to those without, and evidence that there may be subgroups of LBLP patients with and without neuropathic pain in both those clinically diagnosed with sciatica or referred leg pain. Limitations in the available literature have been identified and discussed, and applying the findings of this review to current clinical practice in primary care and in settings similar to primary care should be done with caution.

Future research investigating the prognosis of LBLP patients with and without neuropathic pain is likely to inform patients of likely course over time and will inform decision making in clinical practice. The subsequent chapter reports on the methods and study design used to investigate the epidemiology of neuropathic pain in this patient population.

Chapter Four. Study design and methods

4.1 Introduction

This Chapter outlines the design and methods used in research in the subsequent chapters (Chapters 5 to 9) of this thesis. All of the analyses in the research in this thesis are based on data from a prospective cohort, the Assessment and Treatment of Leg pain Associated with the Spine (ATLAS), led by researchers at Keele University in the UK. A detailed report is provided on the population of interest, LBLP patients consulting in primary care, including a report on the inclusion criteria of the study, the methods used for data collection and a description is provided on the clinical management of patients in the ATLAS study. The definitions of neuropathic pain and selected characteristics used in research in this thesis are given and are followed by a description of the study sample, a report on the response to follow-up and an account on how missing data is dealt within this thesis is provided.

4.2 Data source

ATLAS was a prospective, observational, multi-centred cohort of LBLP patients who consulted and were treated in primary care. The reader is referred to Konstantinou et al. (2012a) for the protocol of the ATLAS study, a brief summary of the study is provided below.

4.3 Population of interest

Patients aged 18 years and over who consulted with their general practitioner (GP) with LBLP, in practices in North Staffordshire and Stoke-on-Trent, were invited to take part in the ATLAS study. Patients were considered to have LBLP if they presented with

leg pain of any duration that spread from the back beyond the gluteal fold to anywhere in the leg. Pain was considered to include unpleasant sensations such as pins and needles or numbness. Patients were excluded from ATLAS if there was suspected serious spinal pathology, previous spinal surgery, pregnancy, they were receiving physiotherapy treatment (or osteopathy, chiropractic) or were under the care of a secondary care consultant for the same condition, and those with serious physical or mental co-morbidity that would prevent them attending the research clinic or undergo the study's procedures, or inability to read and speak English.

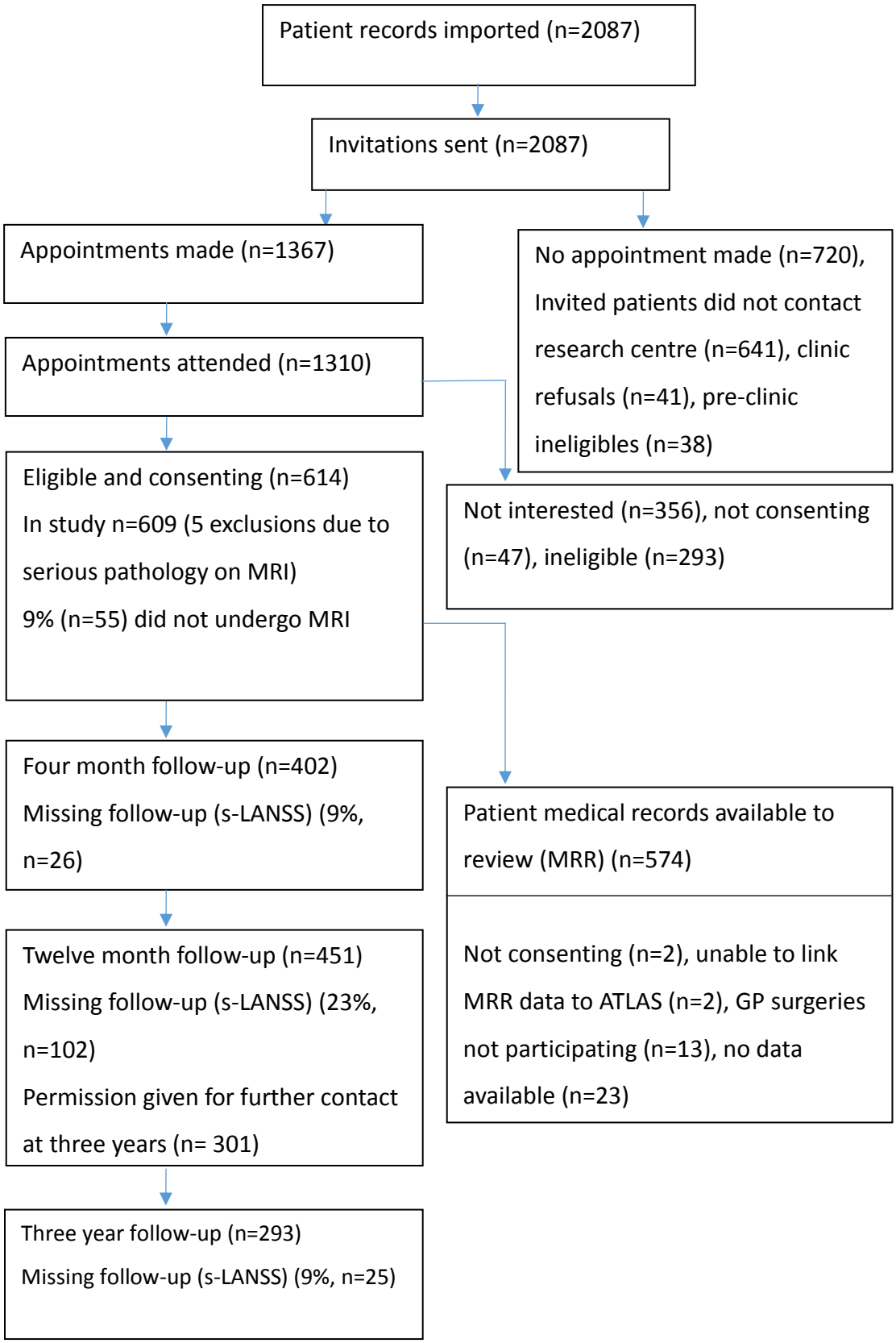
4.4 Recruitment procedure and data collection

Participants were recruited to the ATLAS study between April 2011 and March 2013. Potentially eligible patients were identified at consultation with their GP by the use of Read codes (Hassey et al. 2001). Identified participants were sent information about the study and were invited to telephone the research centre to find out more about the study and to make an appointment at the ATLAS research clinic (a LBLP clinic set in the community). Appointments were offered within 10 working days of participants contacting the research centre; a participant information sheet and a study questionnaire were sent to the participant at this point. At the ATLAS research clinic, all patients were screened for potential eligibility by a study nurse and informed consent was gained if the patient wished to be included in the study. Consent to review patients' medical records was also requested. Full eligibility was determined by a full clinical examination by one of the study's physiotherapists. The recruitment procedures and flow of patients who were eligible and consented to join the ATLAS

study is summarised in Figure 4.1, for further details of the recruitment procedure the reader is directed to the study protocol (Konstantinou et al. 2012a).

Data were collected at baseline at three follow-up points: four months, twelve months and three years. At the twelve month follow-up point patients were asked for consent to be contacted again at three years. At each follow-up point data were collected using postal self-complete questionnaires. Reminders were sent to non-responders at each point. Electronic prescribing and consulting records for consenting study participants were obtained as part of medical record information from the GP practices participating in the ATLAS study for the period of four months before the time of attending the first appointment at the ATLAS research clinic and three years after. All patients in the ATLAS study were invited for a magnetic resonance imaging (MRI) scan within 10 days of attending an assessment at the ATLAS research clinic, except in cases where the test was contraindicated or when an MRI scan was already available in the previous six-months for the same clinical presentation (further details on the reporting of MRI scans in ATLAS is provided in section 4.9.7 (page 132).

Figure 4.1 ATLAS study flow diagram (adapted from Konstantinou et al. (2015))



4.5 Clinical examination

At the ATLAS research clinic, patients underwent a standardised clinical examination by an experienced musculoskeletal physiotherapist to determine full eligibility, diagnosis, and decide a treatment plan. All participants in the ATLAS study were classified as having sciatica or referred leg pain by clinical diagnosis at the time of the clinical examination. Diagnosis was based on the assessor's clinical judgement. In the context of the ATLAS study, the term sciatica is indicative of radicular pain with or without neurological deficits. All physiotherapists in the ATLAS study were given training in the study's procedures. Criteria for clinical diagnosis of sciatica and referred leg pain were agreed following consensus from a Delphi study involving representatives from low back pain disciplines (Konstantinou et al. 2012b). Suggested differentiating signs and symptoms between sciatica and referred leg pain described in the training manual are summarised in Table 4.1 below. There was fair agreement between clinicians when making a diagnosis of sciatica or referred leg pain (Stynes et al. 2015).

Table 4.1 Differentiating signs and symptoms of sciatica and referred leg pain

	Sciatica	**Referred leg pain**
Pain descriptors	Sharp-toothache like, cramping, tingling, burning	Deep-dull ache
Pain distribution	Dermatomal distribution Leg often worse than back Pain often below the knee	Non dermatomal distribution Not often below the knee
Cough/ sneeze/ strain	Often worse with coughing/ sneezing/ straining	Not effected by coughing/ sneezing
Neurodynamic testing	Often positive neurodynamic tests (for example, straight leg raise)	Normal neurodynamic tests
Neurological testing	Variable neurological findings	Normal neurological findings

4.6 Care pathways

Clinical management of patients in the ATLAS study were agreed a priori and are documented in full in the ATLAS protocol ((Konstantinou et al. 2012a), a summary is provided below. Patients in the study received clinical management based on current best clinical evidence and guidelines within the capacity of local NHS facilities and resources. The treatment provided to patients was under the discretion of the treating physiotherapist in consultation with the patient. For those patients where physiotherapy management was indicated, up to six (on average) treatment sessions

(of 30 minutes) were delivered over a six to eight week period. If a patient's symptoms worsened or failed to improve, pathways were in place so that appropriate referrals could be made to a specialist spinal services for further assessment and management including onward referral to spinal surgeons, pain specialists and rheumatologists. Section 4.9.9 provides a detailed report of how the care provided to patients in the ATLAS study was recorded in this thesis.

4.7 Case definitions of neuropathic pain

The research in this thesis presents results based on two different approaches using three definitions of neuropathic pain. For a report on the background to the approaches see Chapter 1, section 1.3.1 (page 10).

4.7.1 Definition based on a case ascertainment tool

To complete the epidemiological description of neuropathic pain in this patient population, the self-report version of Leeds Assessment of Neuropathic Symptoms and Signs (s-LANSS) (Bennett et al. 2005) was used. The maximum score for s-LANSS is 24, this research used a cut-value of 12 (found to be the optimum cut-value for classifying cases of neuropathic pain (Bennett et al. 2005)) to describe patients with "possible" neuropathic pain (Smith et al. 2012a, Bennett et al. 2005). Patients with s-LANSS score of less than 12 were described non-neuropathic pain. Study participants completed s-LANSS as part of the baseline health survey questionnaire, four and twelve months after baseline and also three years after baseline.

4.7.2 Definition based on clinical diagnosis

Cases of neuropathic pain were also determined by clinical diagnosis. This method of determining cases of neuropathic pain was adapted from the NeuPSIG classification system first described by Treede et al. (2008) and which was updated by Finnerup et al. (2016) (See Figure 1.2 (page 11) for a summary of the NeuPSIG classification). Cases of neuropathic pain that could have been described as "unlikely", "possible" and "probable" were identified (see Table 4.2). It was not possible to determine "definite" neuropathic pain because areas of sensory abnormality specific to the painful area were not recorded in this research.

Table 4.2 Neuropathic pain definitions based on clinical diagnosis

Description	**Diagnostic certainty of neuropathic pain**
Clinical diagnosis of sciatica Evidence of possible or clear nerve root compression on MRI scan	Probable
Clinical diagnosis of sciatica Without evidence of possible or clear nerve root compression on MRI scan	Possible
Clinical diagnosis of referred leg pain	Unlikely

Abbreviation: MRI, magnetic resonance imaging

4.8 Data management

The research summarised in Chapters 5 to 9 of this thesis comprises secondary analyses of the ATLAS study data. The majority of data were collected, entered into a

database and cleaned prior to the analyses within this secondary research commencing. Some data had been recorded, either by clinical examination or self-report, but had not been entered in the database for the primary analysis, these included information on pain medication use at baseline and pain pattern. Therefore, data on pain medication use and pain pattern were entered into a Microsoft Excel spreadsheet by the thesis researcher. Checks were completed (one in ten) throughout data entry and any errors or omissions were identified. Once data cleaning was completed, the researcher transferred the data into the statistical software, Stata (see section 4.12 (page 149) for a details on the statistical software used in this thesis).

In preparation for analysis, the thesis researcher visually inspected all variables to determine the number of missing observations, to approximate the distribution and to identify observations that were erroneously coded. Where indicated variables were re-coded in preparation for analysis. For descriptive analysis, some continuous variables (for example data on anxiety and depression using the Hospital Anxiety and Depression Scale (HADS) (see section 4.9.5 (page 128)) were categorised or dichotomised based on the optimal cut-off points for the respective tool. Where possible, this process was done in accordance with existing literature recommendations. The following section (4.9) provides the details of the selected variables.

4.9 Selected characteristics

The analyses in this thesis are based on understanding the association between neuropathic pain and a number of characteristics of interest that were identified from

the published literature and were available within the ATLAS dataset. This section gives a brief description of each of the characteristics obtained from the self-report questionnaires, clinical examination data, MRI and electronic medical records.

4.9.1 Sociodemographic

4.9.1.1 Age and sex

The age (from date of birth) at time of completing the study baseline questionnaire and sex of each participant was obtained from self-report; age was reported as a continuous variable.

4.9.1.2 Socio-economic status

The current job title of each participant, or most recent among those not working, was obtained from the baseline questionnaire and was used as a proxy for socio-economic status (Office of National Statistics 2010). Socioeconomic status, as determined by job title, was collapsed into three main groups: managerial and professional occupations, intermediate occupations, routine and manual occupations. This three-class grouping is a recognised approach for the examination of social class (Rose and Pevalin 2003). Numbers for those who had never worked and the long-term unemployed, were also reported.

4.9.1.3 Smoking status

Participants were asked if they were a current smoker, the required response been either “yes” or “no”. If the participant answered “no”, they were then asked if they had ever smoked (the required response was “yes” or “no”). The responses to the two

questions were amalgamated and reported as one variable for smoking status describing participants who were current smokers, ex-smokers or who had never smoked.

4.9.1.4 Body mass index

Body mass index (BMI) was calculated as a continuous variable in kilograms per metre^2 (kg/m^2).

4.9.2 Health status

Biologically plausible characteristics that may be associated with neuropathic pain were determined from self-report, these were general health and history of other health problems including diabetes, reports of fatigue and sleep difficulties.

4.9.2.1 General health

Patients were asked how they perceived their general health, taken from the Short Form 36 Health Survey, where self-reported general health is reported as either "excellent", "very good", "good", "fair", or "poor" (Ware 2000). General health was reported as four categories, "excellent or very good", "good", "fair", or "poor".

4.9.2.2 Co-morbidities

Co-morbidities were recorded from a list of five possible conditions (chest problems, heart problems, hypertension, diabetes, circulation in legs). Comorbidities were categorised as "no other health problems", "one or other health problems", or "two or more health problems". Painful diabetic neuropathy is a neuropathic condition and the

proportion of patients who self-reported diabetes in the sample was presented separately.

4.9.2.3 Fatigue and difficulties with sleep

Fatigue and difficulties with sleep were taken from a question about the patient's identity with their pain from an adapted version of the Illness Perceptions Questionnaire (IPQ-R) (Moss-Morris et al. 2002). Patients were presented with a statement, "tell us whether you have experienced either of these symptoms because of your back and/ or leg problem: 1) fatigue and 2) sleep difficulties" where the required response was either "yes" or "no".

4.9.3 Pain characteristics

Pain intensity, duration, location, pain pattern (constant or intermittent pain) and the presence of widespread pain were self-reported and recorded for the purposes of this study. Information on pain characteristics (pain intensity, duration, widespread pain) were obtained from self-report questionnaires, additional information (pain location and pattern) was derived from the clinical examination.

4.9.3.1 Pain intensity

At baseline, back pain intensity was determined using a pain index by averaging three 0 to 10 numerical rating scales for least, current and usual back pain over the previous two weeks (Dunn et al. 2010). This question was repeated for baseline leg pain intensity and was presented as a distinct characteristic to back pain intensity. At follow-up, to determine whether patients continued to have leg pain the following

question was presented to patients, “Has the pain from your back spread down your leg or legs in the last two weeks?” The required response was either “yes” or “no”. Those patients who responded “yes” (and were deemed to be having leg pain at follow-up) were then asked to rate their least, current and usual leg pain, as at baseline. At follow-up, leg pain intensity and separately, back pain intensity, were determined in the same way as at baseline by taking the mean of least, current and usual back pain over the previous two weeks. The highest pain intensity was determined to be the highest of either mean back pain intensity or mean leg pain intensity.

4.9.3.2 Pain duration

Information on back pain duration was derived from the question, “Have you had this current bout/episode of back pain for….” to which there were seven discrete response categories, “less than 2 weeks”, “2 to 6 weeks”, “6 to 12 weeks”, 3 to 6 months”, “7 to 12 months” and “more than 12 months”. For this study, duration was categorised into three groups, less than six weeks, six to twelve weeks and greater than three months. The question was repeated for leg pain and presented distinct from back pain duration. The response to this question relies on accurate recall of pain duration and there is some evidence (Jordan et al. 2006) that self-reported duration of pain is a reasonable approach to take in epidemiological surveys.

4.9.3.3 Widespread pain

Widespread pain for this research was defined as pain present above and below the waist, in the right- and left-hand sides of the body and in the axial skeleton. This

satisfies the American College of Rheumatology 1990 criteria for fibromyalgia (Wolfe et al. 1990). Widespread pain was derived from a single question. Patients were asked, “In the past 4 weeks have you had pain that has lasted for one day or longer in any part of your body, other than your back or legs” and they were asked to indicate this by shading their painful area on a full body manikin (front and back views). The manikin was divided into 44 mutually exclusive areas, and these were recorded by using a standard transparent template marked with borders (Lewis et al. 2002). This method for detecting widespread pain has previously been used (McBeth et al. 2014) and has shown to be valid and reliable (Lacey et al. 2005).

4.9.3.4 Pain location

Three characteristics were recorded during clinical examination that described the location of pain including the part with worse pain: presence of pain below the knee, presence of pain in both legs and whether leg pain was worse than back pain. Patients were asked whether their pain extended below the knee, this was recorded by the physiotherapist on a full body chart and recorded as dichotomous answers, “yes” or “no” for both the right and left legs. For analysis, results for the presence of pain below the knee in one or both legs, were combined and reported as one variable. The body chart also described whether patients had pain in both legs, this was reported as dichotomous answers, “yes” or “no”. During the clinical assessment patients were asked whether the leg pain was worse than the back pain or not, leading to dichotomous answers and “yes” or “no” respectively.

4.9.3.5 Pain pattern

Information on whether the pain pattern was constant or intermittent was derived from the clinical examination. Patients were asked whether their pain in the back, thigh or lower leg (depending on their presenting pain) was constant to which the physiotherapist circled ("yes") where the pain was constant, if any. Similarly, patients were then asked if their pain was intermittent and it was recorded in the same way as for constant pain. The responses were categorised into "yes" or "no" for constant and intermittent symptoms and were reported as the proportion describing constant symptoms.

4.9.3.6 Pain quality

Whether or not patients reported burning pain quality was derived from the fifth individual item of s-LANSS. Patients were asked if "in the area where you have pain, does your skin feel hot like a burning pain?" The responses were categorised as "I don't have burning pain (no)", or "I get burning pain often (yes)".

4.9.4 Limitations in activities, participation and risk of persistent disability

Three self-report measures were used to capture limitations in activities, participation and risk of persistent disability due to LBLP.

4.9.4.1 LBLP-related disability

LBLP-related disability was measured with the Roland Morris Disability Questionnaire (RMDQ) (Roland and Morris 1983) leg version (Patrick et al. 1995) which has 23 items

scored from 0 to 23 with higher scores indicating higher disability. RMDQ was reported as a continuous variable.

4.9.4.2 Interference with work performance

Information on work interference because of back or leg pain were derived from the baseline questionnaire using a 0 to 10 numerical rating scale. Patients were asked “on average, to what extent has your back or leg pain affected your performance at work since your back or leg pain started?” The patients rated their work performance where 0 is “not at all” and 10 is “the pain is so bad that I am unable to do my job” (Kigozi et al. 2014). Pain interference with work performance was only applicable to those currently working, it was reported on a continuous scale.

4.9.4.3 Risk of persistent pain-related disability

The Keele STarT Back screening tool (Hill et al. 2008) is a simple tool that helps clinicians identify modifiable risk factors (biomedical and psychological) for back pain-related disability. The nine-item tool consists of eight statements that the patient can either “agree” or “disagree” with and one question (“overall, how bothersome has your back pain been in the last two weeks?) to which the patient can answer using a five-point categorical scale ranging from “not at all” to “extremely”. STarT Back is scored on a nine-item scale and stratifies patients as at low, medium or high risk of persistent disability because of LBP. Low, medium and high risk categories for STarT Back were reported in the investigations in this thesis.

4.9.5 Psychological characteristics and illness perceptions

Four different self-report scales were used to report psychological variables and illness perceptions, these were Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith 1983), two domains from IPQ-R (Moss-Morris et al. 2002) and Pain Self-Efficacy Questionnaire (PSEQ) (Nicholas 2007).

4.9.5.1 Symptoms of anxiety and depression

HADS consists of two scales (one for anxiety, one for depression) each with seven statements with a maximum possible score of 21 on each scale measuring the severity of anxiety and depression. Statements include, “I feel tense or wound up”, or “worrying thoughts go through my mind” to which the patient confirms or refutes on a four-point categorical scale (scored 0 to 3), “most of the time”, “a lot of the time”, “from time to time occasionally”, or “not at all”. Higher scores indicate higher levels of anxiety and depressive symptoms. HADS anxiety is categorised as normal (scores 0 to 7), possible/mild cases (scores 8 to 10), probable/moderate cases (scores 11-15) and severe cases (scores > 16). For this study, scores for HADS moderate and severe cases were amalgamated and reported as one group as few patients in the study scored more than 16; the same categories were set for the depression scale. Symptoms of anxiety and depression using HADS were reported for descriptive purposes categorically and separately on a continuous scale.

4.9.5.2 Illness perceptions

The two domains from IPQ-R were personal control and timeline (acute to chronic). For both domains patients were presented with statements and five levels to which

they agree with a specific statement (“strongly agree”, “agree”, “neither agree or disagree”, “disagree” or “strongly disagree”). The statement related to personal control was, “There is a lot which I can do to control my back and / or leg symptoms” and timeline, “My back and, or leg problem will last for a long time”. Both domains were then categorised further into either “agree or strongly agree” versus “disagree or strongly disagree”.

4.9.5.3 Pain self-efficacy

Pain self-efficacy is a concept developed by Bandura (1977). Self-efficacy is the degree to which an individual believes they can successfully cope with difficult situations, in the context of this research, the degree to which a patient has confidence in carrying out normal activities and tasks of daily living despite having pain. This research used the pain self-efficacy questionnaire (PSEQ) to determine the confidence of an individual to perform a range of tasks and the confidence with more generalised constructs such as coping with pain. It consists of 10 statements (for example, “I can enjoy things, despite the pain” to which the individual answers on a 0 to 6 categorical scale, where 0 represents “not at all confident” and 6 represents “completely confident”. PSEQ is scored on a 0 to 60 scale, where higher scores reflect stronger self-efficacy beliefs. It was retained as continuous scale for the purposes of this study.

4.9.6 Neurological examination

The neurological examination was carried out as part of the clinical examination as recommended in LBP guidelines (Chou et al. 2007) and specialist books (for example Examination of the Lumbar Region in Neuromusculoskeletal Examination and

Assessment (Mercer and Finucane 2011) (pages 329 to 330). This included the components described below.

4.9.6.1 Muscle strength

Muscle strength was tested in relation to specific lower limb myotomes according to the 6-point grading scale for manual muscle testing that is widely described (for further details of how muscle testing was carried out see Principles of Manual Muscle Testing in Hislop and Montgomery (2002) (pages 1 to 8)) where:

0. No visible flicker of movement or contraction
1. Flicker of movement
2. Full active movement with gravity counterbalanced
3. Full active movement against gravity but not applied resistance
4. Full active movement against gravity and some applied resistance
5. Full active movement against gravity and strong resistance.

For this research, the grades 0 to 3 were amalgamated into one category and three categories were reported, “0 to 3/5”, “4/5” and “5/5”.

4.9.6.2 Reflex change

Any change in either knee or ankle reflexes were recorded and categorised into normal, slightly reduced, significantly reduced and absent. The categories for significantly reduced and absent reflexes were then amalgamated.

4.9.6.3 Sensory loss or gain

4.9.6.3.1 Sensory loss

Sensation to pin-prick (using semi-sharp, single use neurological examination pins called Neurotip) specific to dermatomes in the lower limb(s) were described as “normal”, “reduced pin-prick sensation”, “loss of pin-prick sensation” and “total anaesthesia”. Sensation to pin-prick is reported in Chapter 5 and presented as one of three categories, “normal”, “reduction of pin-prick sensation” or “loss of pin-prick sensation” where “loss of pin-prick sensation” and “total anaesthesia” were amalgamated into one category. In Chapters 7 to 9 the variable reporting sensation to pin-prick was amalgamated further and was presented as a binary variable, “normal” or “reduction or loss of pin-prick sensation”.

4.9.6.3.2 Sensory gain

Hyperalgesia is an increased pain response to painful stimuli and allodynia is pain response to normally non-painful stimuli, both considered to be gains of sensory function. The presence of allodynia was recorded in response to light touch with one finger and hyperalgesia was recorded when the reaction to pin-prick was extreme. The presence or absence of either hyperalgesia or allodynia were recorded and presented as one variable.

4.9.6.4 Presence of pins and needles

The presence of pins and needles was derived from the clinical examination and was recorded as either “yes” or “no” as reported by the patient.

4.9.6.5 Colour change

Whether or not patients reported colour change in the painful area was derived from the second individual item of s-LANSS. Patients were asked if in the area of pain the skin changes colour (more mottled or more red) when the pain is particularly bad. The responses were categorised as “The pain does not affect the colour of my skin (no)”, or “I have noticed that the pain does make my skin look different (yes)”.

4.9.6.6 Neural tension tests

Neural tension tests examine the elongation of nerves in a limb (Elvey 1997). In this research three tests that are routinely used in clinical practice were used to detect the presence of neural tension. These tests were the straight leg raise, which is carried out by passively elevating the leg with the knee extended; the femoral stretch where the patient is in a prone position, knee passively flexed to the thigh and the examiner passively extends the hip to increase the stretch on the femoral nerve; and the slump test, where the patient sits head forward, leg outstretched and toes point upwards, the examiner gently eases the patient forward to increase the stretch on the sciatic nerve. Reproduction of the patient’s leg pain is considered positive (Butler 1991). Any positive neural tension test was considered to indicate the presence of neural tension (“yes” or “no”).

4.9.7 Neuroimaging

MRI is the best available diagnostic imaging modality for LBLP as it provides excellent resolution of spinal structures allowing for assessment of nerve root compression. Patients had an MRI scan, except in contra-indicated cases or when the patient did not

wish to have a scan. MRIs were scored by a single assessor, a Consultant Musculoskeletal Radiologist in the NHS Trust Hospital in Stoke-on-Trent. The assessor was blind to any clinical information relating to the patient's symptoms other than the clinical presentation (low back and leg pain), the painful leg(s) were not disclosed. A summary report on the MRI scan was provided indicating the presence or absence of definite or possible nerve root compression by lumbar spinal level (lumbar levels L3/4, L4/5 and L5/S1) and by side (right and/or left). The reason(s) for the nerve root compression were also given (for example, bulge, protrusion, sequestration or stenotic features) as is normal practice in radiological reporting (Konstantinou et al. 2015). Evidence of clear or possible nerve root compression on MRI was amalgamated and reported as a binary variable ("yes" or "no").

4.9.7.1 Procedure for reporting MRI to patients

When the MRI results were available, the physiotherapist discussed these with the patient. Interpretation of MRI results and language used to convey MRI results was included in the training the study physiotherapists received. Four of the study physiotherapists were also spinal extended scope practitioners and the ATLAS cohort was conducted under the auspices of the local Spinal Interface Service, with clinicians from this service contributing to MRI interpretation as needed, for both patients and GPs. As per normal clinical practice, GPs received a copy of the MRI report alongside the clinic letter when a patient completed their treatment and were discharged to the care of their GP.

4.9.8 Health care use

Health care use in this thesis is reported based on data collected in two ways. Firstly, the number of physiotherapy treatment sessions that patients attended were recorded by the ATLAS study team, as were the number of referrals made by the study's physiotherapists to specialist spinal services. These were amalgamated and recorded as one variable with three categories for "0 to 2 physiotherapy sessions", "3 or more physiotherapy sessions" and "onward referrals". It was not known what proportion of patients were either lost to follow-up during physiotherapy treatment or who were discharged following a complete course of treatment. Secondly, the number of consultations that patients made with their GP or with specialist nurse practitioners in primary care was determined from electronic medical records.

4.9.8.1 Pain medications

This thesis describes the pain medication use in LBLP patients with neuropathic pain with data collected in two ways. Firstly, research in Chapter 5 (prevalence and baseline characteristics) describes the pain medication use of LBLP patients with and without neuropathic pain derived from information recorded in the clinical assessment, and then Chapter 9 (prescribing patterns of pain medication) describes the patterns of pain medications prescribed to patients with neuropathic pain derived from primary care electronic prescribing and consulting records for patients in the Atlas study. Regarding pain medications reported in Chapter 5, the assessing physiotherapist recorded the patients self-reported drug history, both prescribed medication and those bought over the counter were recorded during the clinical consultation, only the name of the

medication was recorded. For patients who consented to having their electronic prescribing and consulting records reviewed (see Figure 4.1 (page 115) for a summary of those patients who consented to a review of medical and prescription records), the name, dosage and quantity prescribed to an individual patient was recorded.

In both chapters, medication was categorised into a number of groups based on recommendations from existing literature (see Table 4.3 for details on how pain medication was categorised in this thesis). The first group of pain medications was the group recommended for first line treatment of neuropathic pain (Amitriptyline, Gabapentin, Pregabalin or Duloxetine) based on evidence from UK guidelines for non-specialist settings (NICE CG173 2013). The second to fourth groups were classified according to equipotent medications based on a previously published categorisation system for pain medication in UK primary care (Bedson et al. 2013). The second group were basic analgesics, the third were opioids, and the fourth were non-steroidal anti-inflammatory medications. Opioids were categorised further for research in Chapter 9 by the strength of the opioids prescribed. These groups comprised weak to moderate strength opioids and strong to very strong opioids, made possible given their specific names, dosages and quantities were recorded. Nefopam is not an opioid (Kim et al., 2014) but it is considered to be equipotent to opioids with moderate strength and was classified along with opioids of weak to moderate strength. The fifth group of medications was skeletal muscle relaxants based on evidence that these drugs are associated with a reduction in pain intensity in acute episodes of LBP with or without leg pain (Qaseem et al. 2017). Groups one to five were mutually exclusive of one

another. Tramadol is not considered a first line neuropathic pain medication but it is a recommended medication for patients with acute episodes of neuropathic pain (NICE CG173 2013). For this reason, for research in Chapter 9, Tramadol was categorised depending on dosage into either weak or moderate strength opioid (Group 3a) or strong to very strong opioid (Group 3b) and into a sixth group of pain medications, a broader group of neuropathic pain medications.

Table 4.3 Categorisation of pain medications in this thesis

Group	Description	Chapter 5	Chapter 9	
		Prevalence and characteristics	**Prescribing patterns of pain medications**	
1	**First-line neuropathic pain medication**	Amitriptyline Duloxetine Gabapentin Pregabalin	Amitriptyline Duloxetine Gabapentin Pregabalin	
2	**Basic analgesia**	Paracetamol Topical Ibuprofen Topical Diclofenac	Paracetamol Ibuprofen (200mg-400mg) Topical Ibuprofen, Topical Diclofenac	
3	**Opioids**	Buprenorphine Co-codamol Co-dydramol Co-proxamol Codeine Dihydrocodeine Nefopam	**3a. Weak to moderate opioids** (+/- combination with paracetamol)	Buprenorphine (<10mcg/hour) Co-codamol Co-dydramol Co-proxamol Codeine (<15mg) Dihydrocodeine (<30mcg) Tramadol (<50mg) Nefopam*

Group	Description	Chapter 5	Chapter 9	
		Prevalence and characteristics	Prescribing patterns of pain medications	
		Morphine Tramadol Oxycodone	**3b. Strong to very strong opioids**	Buprenorphine (>10mcg/hour) Morphine Tramadol (≥50mg) Oxycodone Dihydrocodeine (≥30mg) Codeine (≥30mg)
4	**Non-steroidal anti-inflammatory medication**	Diclofenac Etoricoxib Ibuprofen Meloxicam Naproxen	Diclofenac Etoricoxib Ibuprofen (>400mg) Meloxicam Naproxen	
5	**Skeletal muscle relaxants**	Diazepam	Diazepam	
6	**Neuropathic pain medication**		Tramadol Amitriptyline Duloxetine Gabapentin Pregabalin	

Abbreviations: mcg, microgram. mg, milligram

* Nefopam acts through central mechanisms distinct to the action of opioids but is considered to be equipotent with opioids of moderate strength

4.10 Study sample

4.10.1 Completion of baseline data and clinical examination

In total, 2087 potentially eligible patients were identified at the time of a primary care consultation and were invited to the ATLAS study, of which, 641 did not contact the research centre to make an appointment. 1310 potentially eligible patients made and attended appointments (Figure 4.1, see p115). After attending the first appointment, the absence and/or recovery from leg pain was the most common reason for ineligibility (n=136 out of 293) following the baseline assessment in the ATLAS clinic. Please see Konstantinou et al. (2015) for further details of the flow through the study and detailed reasons for excluding potential patients before or following the baseline assessment.

Those who were ineligible, or were not interested in participating in the study were more often male (63% vs 57%), slightly older (mean age 55 vs 50 years) and slightly more often from the least deprived area tertile (36% vs 31%) compared to those who did take part. These are common findings when comparisons have been made in previous literature (Konstantinou et al., 2015).

A total of 609 LBLP patients who completed baseline assessment were eligible, provided consent and were included in the ATLAS study. At baseline, three patients did not complete all seven of the questions that make up s-LANSS; all 609 patients were assessed for a clinical diagnosis. Nine percent of patients (n=55) did not undergo MRI, most cited claustrophobia as the reason for declining an MRI, four had contraindications for the procedure (Konstantinou et al., 2015). Less than 5% of other

baseline characteristics were missing. At baseline, self-reported general health, belief that leg and/or back pain symptoms will last a long time and back pain duration all had less than 1% (n=4) missing observations. Up to 4% (n=26) of observations were missing for socio-economic status, risk of persistent disability because of back pain/leg pain (STarT Back), pain self-efficacy (PSEQ) and leg pain duration at baseline. All other baseline characteristics were complete.

4.10.2 Response to follow-up

Of the 609 patients who completed baseline questionnaires, 402 (66.0%) completed the questionnaire at four-months, 450 (73.9%) at twelve months and 293 (48.1%) at three-years. Of the 402 patients who were followed up at four-months, 26 (6%) patients did not complete or partially completed s-LANSS. There was incomplete s-LANSS data at both twelve months (102 out of 450 cases, 23%) and at three-years (25 out of 293, 9%). Patients who responded to follow-up at four-months were older (54 years compared to 42 years), fewer scored 12 or greater on s-LANSS (45% compared to 55%), slightly higher proportion had a clinical diagnosis of sciatica (77% compared to 70%) and they had slightly lower LBLP-related disability (mean RMDQ 12.1 compared to 13.7) at baseline. This was consistent at both twelve-months and three-years. Patients who responded to follow-up questionnaires self-reported fewer co-morbidities and were more likely to agree or strongly agree with the statement “what I can do determines whether back and/or leg pain gets better”, and less likely to believe that either their leg or back pain symptoms would last for a long time. See Table 4.4 for

a detailed description of the baseline characteristics of patients who either responded to the follow-up questionnaires or were lost to follow-up at each time point.

Table 4.4 Baseline characteristics of participants followed-up and lost to follow-up

Key baseline characteristics		4 Months		12 Months		3 Years	
		Followed up (n=402; 66%)	*Lost to follow-up (n=207; 34%)*	*Followed up (n=450; 74%)*	*Lost to follow-up (n=159; 26%)*	*Followed up (n=293; 48%)*	*Lost to follow-up (n=316; 52%)*
Sociodemographic characteristics							
Female		246 (61.7)	136 (65.7)	294 (65.8)	88 (55.4)	183 (62.9)	199 (63.2)
Age, mean (SD)		54.2 (13.0)	42.3 (12.1)	52.9 (13.2)	42.5 (13.0)	54.2 (12.7)	46.4 (13.9)
Socio-economic status	Higher managerial, administrative and professional occupations	90 (23.2)	38 (18.8)	102 (23.7)	26 (16.4)	72 (25.7)	56 (18.1)
	Intermediate occupations	103 (26.6)	54 (26.7)	110 (25.5)	47 (29.6)	70 (25.0)	87 (28.1)
	Routine and manual occupations	182 (46.9)	100 (49.5)	204 (47.3)	78 (49.1)	133 (47.5)	149 (48.1)

Key baseline characteristics		4 Months		12 Months		3 Years	
		Followed up (n=402; 66%)	*Lost to follow-up (n=207; 34%)*	*Followed up (n=450; 74%)*	*Lost to follow-up (n=159; 26%)*	*Followed up (n=293; 48%)*	*Lost to follow-up (n=316; 52%)*
	Never worked and long-term unemployed	13 (3.4)	10 (5.0)	15 (3.5)	8 (5.0)	5 (1.8)	18 (5.8)
Health status							
Co-morbidities*	No other health problems	226 (56.6)	144 (69.6)	261 (58.4)	109 (68.6)	167 (57.4)	203 (64.4)
	One other health problem	111 (27.8)	46 (22.2)	124 (27.7)	33 (20.8)	86 (29.6)	71 (22.5)
	Two or more other health problems	62 (15.5)	17 (8.2)	62 (13.9)	124 (27.7)	38 (13.1)	41 (13.0)
Self-reported general health	Excellent/ very good	101 (25.3)	44 (21.4)	112 (25.1)	33 (20.8)	74 (25.4)	71 (22.6)
	Good	111 (27.8)	60 (29.1)	122 (24.4)	49 (30.8)	74 (25.4)	97 (30.9)

Key baseline characteristics		4 Months		12 Months		3 Years	
		Followed up (n=402; 66%)	*Lost to follow-up (n=207; 34%)*	*Followed up (n=450; 74%)*	*Lost to follow-up (n=159; 26%)*	*Followed up (n=293; 48%)*	*Lost to follow-up (n=316; 52%)*
	Fair	157 (39.4)	82 (39.8)	179 (40.1)	60 (37.7)	122 (41.9)	117 (37.3)
	Poor	30 (7.5)	20 (9.7)	33 (7.4)	17 (10.7)	21 (7.2)	29 (9.2)
Pain characteristics							
Back pain intensity (0-10), mean (SD)		5.2 (1.6)	5.6 (1.6)	5.2 (1.6)	5.7 (1.6)	5.1 (1.6)	5.4 (1.6)
Leg pain intensity (0-10), mean (SD)		5.2 (2.4)	5.3 (2.3)	5.2 (2.4)	5.4 (2.4)	5.1 (2.4)	5.3 (2.4)
Duration of back pain symptoms in current episode	Less than 6 weeks	148 (37.2)	69 (33.5)	168 (37.8)	49 (30.8)	113 (39.1)	104 (33.0)
	6 to 12 weeks	84 (21.1)	41 (19.9)	94 (21.1)	31 (19.5)	59 (20.4)	66 (21.0)
	> 3 months	166 (41.7)	96 (46.6)	183 (41.1)	79 (49.7)	117 (40.5)	145 (46.0)
Duration of leg pain	Less than 6 weeks	164 (42.8)	87 (44.2)	195 (45.5)	56 (37.1)	129 (45.9)	122 (40.8)

Key baseline characteristics		4 Months		12 Months		3 Years	
		Followed up (n=402; 66%)	*Lost to follow-up (n=207; 34%)*	*Followed up (n=450; 74%)*	*Lost to follow-up (n=159; 26%)*	*Followed up (n=293; 48%)*	*Lost to follow-up (n=316; 52%)*
symptoms in current episode	6 to 12 weeks	81 (21.2)	38 (19.3)	85 (19.8)	34 (22.5)	52 (18.5)	67 (22.4)
	> 3 months	138 (36.0)	72 (36.6)	149 (34.7)	85 (19.8)	100 (35.6)	110 (36.8)
Limitations in activities and risk of persistent disability							
RMDQ, mean (SD)		12.1 (5.7)	13.7 (5.6)	12.1 (5.7)	14.1 (5.5)	12.0 (5.7)	13.2 (5.7)
Pain interference with work (0=10), mean (SD) [†]		5.5 (3.0)	6.5 (2.6)	5.6 (3.0)	6.4 (2.7)	5.4 (3.1)	6.2 (2.8)
Risk of persistent	Low risk	60 (15.4)	22 (11.0)	64 (14.9)	18 (11.5)	44 (15.8)	38 (12.4)

Key baseline characteristics		4 Months		12 Months		3 Years	
		Followed up (n=402; 66%)	*Lost to follow-up (n=207; 34%)*	*Followed up (n=450; 74%)*	*Lost to follow-up (n=159; 26%)*	*Followed up (n=293; 48%)*	*Lost to follow-up (n=316; 52%)*
disability (STarT Back)							
	Medium risk	188 (48.7)	686 (43.0)	211 (49.1)	63 (40.4)	142 (50.9)	132 (43.0)
	High risk	138 (35.8)	92 (46.0)	155 (36.1)	75 (48.1)	93 (33.3)	137 (44.6)
Psychological characteristics and illness perceptions							
HADS (0-21) (depression), mean (SD)		6.0 (3.9)	7.1 (4.2)	6.0 (3.9)	7.4 (4.2)	6.2 (3.9)	6.5 (4.1)
HADS (0-21) (anxiety), mean (SD)		7.5 (4.1)	8.3 (4.2)	7.5 (4.1)	8.7 (4.1)	7.4 (4.1)	8.2 (4.1)
PSEQ (0-60), mean (SD) ‡		36.1 (14.7)	30.4 (13.5)	35.5 (14.2)	30.4 (14.7)	35.6 (14.7)	32.9 (14.3)

Key baseline characteristics		4 Months		12 Months		3 Years	
		Followed up (n=402; 66%)	*Lost to follow-up (n=207; 34%)*	*Followed up (n=450; 74%)*	*Lost to follow-up (n=159; 26%)*	*Followed up (n=293; 48%)*	*Lost to follow-up (n=316; 52%)*
IPQR- Illness perceptions	Timeline "back/leg pain will last for a long time" (agree or strongly agree)	209 (52.4)	135 (65.2)	239 (53.5)	105 (66.0)	145 (49.8)	199 (63.2)
	Personal control "what I can do determines whether back/leg pain gets better" (agree or strongly agree)	156 (39.3)	66 (32.2)	179 (40.3)	43 (27.2)	127 (43.8)	95 (30.5)

Key baseline characteristics	4 Months		12 Months		3 Years	
	Followed up (n=402; 66%)	*Lost to follow-up (n=207; 34%)*	*Followed up (n=450; 74%)*	*Lost to follow-up (n=159; 26%)*	*Followed up (n=293; 48%)*	*Lost to follow-up (n=316; 52%)*
Neuroimaging						
Clear or possible nerve root compression on MRI	212 (57.9)	83 (45.6)	230 (56.1)	65 (47.1)	160 (59.5)	135 (48.4)
Neuropathic pain definitions						
Clinical diagnosis of sciatica§	306 (76.7)	144 (69.6)	336 (75.2)	114 (71.7)	221 (76.0)	229 (72.7)
s-LANSS ≥12§	180 (45.1)	113 (54.6)	209 (46.8)	84 (52.8)	135 (46.4)	158 (50.2)

All figures are frequencies (percentages) unless stated otherwise as mean (SD), denominator varies for some characteristics due to missing data or not applicable case.
Abbreviations: HADS, Hospital Anxiety and Depression scale. IPQ-R, Illness Perceptions Questionnaire-revised. PSEQ, Pain Self-efficacy Questionnaire. RMDQ, Roland Morris Disability Questionnaire leg version. SD, standard deviation. S-LANSS, self-report version of the Leeds Assessment of Neurological symptoms and Signs neuropathic pain scale

*Co-morbidities include self-reported chest problems, heart problems, raised blood pressure, diabetes, and circulation problems in the leg

† Applicable to those currently in paid job

‡ Higher scores on PSEQ reflect stronger self-efficacy beliefs

§ Patients with a clinical diagnosis of sciatica and/or an s-LANSS score ≥12 are described as having “possible” neuropathic pain

4.11 Missing data

Section 4.10.3 highlights some differences in baseline characteristics between patients who responded to questionnaires at follow-up compared to those who did not, these differences can lead to potential bias (von Elm et al. 2007, Sterne et al. 2009). Missing data can also lead to imprecision because of a loss of power (Horton and Kleinman 2007). In this thesis methods used to deal with missingness were based on likelihood approaches (Chapter 6 and 8) and multiple imputation (MI) (Chapter 7, 8 and 9). MI is advocated (Vandenbroucke et al. 2014) for replacing the missing observations with plausible estimates creating a predefined number of imputed datasets. The following section (section 4.11.1) describes the assumptions of MI and the details of the imputation model. Sensitivity analyses were carried out comparing analyses using complete cases and those using imputed data, the results of each sensitivity analysis is summarised within each chapter where missing data could have caused some concern.

4.11.1 Multiple imputation

MI assumes that data are missing at random, that is missing values are related to other observed characteristics. Data from all 609 patients was used to impute missing values on the outcomes used in this thesis (these were neuropathic pain based on s-LANSS, pain intensity using the highest of three 0 to 10 NRS for leg and back pain intensity and LBLP-related disability using RMDQ) and baseline characteristics with missing data. Characteristics that were associated with missingness at each of the three follow-up points were included in the imputation model, as well as characteristics that were consistently associated with the three definitions of neuropathic pain at baseline and

all characteristics that were included in any multivariable models. Checks were made for collinearity between characteristics before entering them into the final imputation model. Multiple imputation by chained equations (MICE) (van Buuren and Oudshoorn 2000) was used to generate the imputations. Imputation of continuous variables was based on predictive mean matching which combines standard linear regression with the nearest neighbour imputation approaches. Imputation of binary variables was based on logistic regression while that of ordinal variables was based on ordered logistic regression. Using MI, missing values are imputed *M* times based on a rule of thumb, where *M* is at least equal to the percentage of incomplete cases (White et al. 2011). In this research, a large proportion of the primary end-point which was neuropathic pain (defined using s-LANSS) was missing. At three-years, 341 observations for s-LANSS were either completely or partially missing (56.0%) therefore 60 imputed sets of data were created. The 60 multiply-imputed sets were combined to give a single mean estimate according to Rubin's rules (Rubin 1987).

4.12 Statistical software

All statistical analyses in this thesis were performed using Stata version 14.0 (Stata Corporation, College Station, Texas, USA). The Stata command *impute* was used to generate the imputed datasets and the *mi* procedure was used to analyse the imputed datasets. All generated variables and analytic code were prepared and stored in Stata do-file format. This allows for replication and storage of data for future reference. Specific details of analysis are presented in the methods and results sections of Chapter 5 through to Chapter 9.

4.13 Summary

The ATLAS study is a three year prospective observational cohort of LBLP patients who consulted with their GP in primary care. Investigations undertaken in Chapters 5 to 9 of this thesis were nested in this programme of work. This chapter outlined the ATLAS study design, methods, data collection procedures and methods used to account for missing data. The next chapter presents the first analysis investigating the prevalence and characteristics of this patient population with and without neuropathic pain.

Chapter Five. Prevalence and characteristics of neuropathic pain in primary care patients with low back-related leg pain

5.1 Introduction

Previous chapters of this thesis have highlighted gaps in the evidence from epidemiological research, including a description of the characteristics of patients with low back-related leg pain (LBLP) of neuropathic nature (see Chapter 3 for results of a systematic review of the literature). This chapter describes the prevalence of neuropathic pain in LBLP patients who consulted their GP in practices participating in the ATLAS cohort study in North Staffordshire and Stoke-on-Trent, UK, and the characteristics of those with and without neuropathic pain. Comparisons are made between the results of this research and relevant literature, and the clinical implications of these findings are discussed.

5.2 Aims and objectives

5.2.1 Overall aim

To provide point prevalence estimates and describe the characteristics of LBLP primary care patients with neuropathic pain.

5.2.2 Objectives

1. To provide estimates of the point prevalence of neuropathic pain in LBLP patients seeking treatment in primary care.

2. To describe the baseline characteristics of LBLP patients with neuropathic pain, defined by case ascertainment tools and clinical examination, compared to those without neuropathic pain.

3. To examine the association between baseline characteristics of LBLP patients and neuropathic pain defined by case ascertainment tools and clinical examination.

5.3 Methods

A full description of the data source, population of interest, methods used to identify cases of neuropathic pain and a description of the selected variables have been described previously in this thesis (see Chapter 4, Study design and methods) and are summarised below in sections 5.3.1 to 5.3.3.

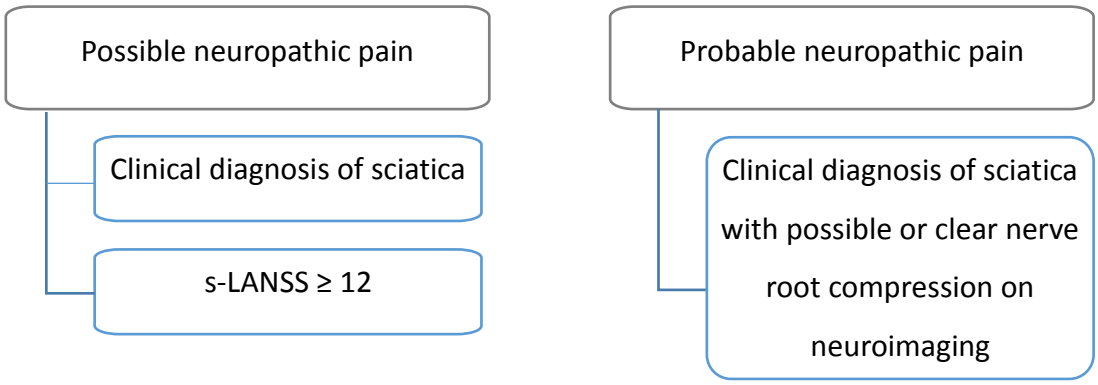
5.3.1 Study design

The research presented in this chapter is based on a cross-sectional, secondary analysis of baseline characteristics of patients in a prospective treatment cohort study of LBLP patients who consulted with their GP in primary care (ATLAS cohort).

5.3.2 Neuropathic pain definitions

Neuropathic pain cases were identified using two different approaches and three definitions (summarised in Figure 5.1), for a full description of each of the three definitions used see Chapter 4, section 4.7 (page 118).

Figure 5.1 Neuropathic pain definitions, grouped by certainty of definition



Abbreviation: s-LANSS, self-report version of Leeds Assessment for Neurological Symptoms and Signs neuropathic pain scale.

5.3.3 Selected characteristics of interest

The analyses in this chapter describe key characteristics of LBLP patients with and without neuropathic pain that were identified from the published literature and were available within the ATLAS dataset. The key characteristics used for research in this chapter are summarised in table 5.1.The reader is referred to Chapter 4 for a detailed report on each of the characteristics reported below.

Table 5.1 Summary of key characteristics used to describe patients with neuropathic pain medication in research in chapter five.

Baseline characteristics	Responses on categorical scale	Continuous scale
Sociodemographic characteristics		
Female sex	Yes	-
Age	-	Years
Socio-economic status	Higher managerial, administrative and professional occupations	-
	Intermediate occupations	-
	Routine and manual occupations	-
	Never worked and long-term unemployed	-
Smoking status	Never	-
	Ex-smoker	-
	Current	-
BMI	-	Kg/m^2
Health status		
Co-morbidities*	No other health problems	-
	One other health problem	-
	Two or more other health problems	-
	Self-reported diabetes	-

Self-reported general health	Excellent/ very good	-
	Good	-
	Fair	-
	Poor	-
Fatigue	Yes	-
Sleep difficulties	Yes	-
Pain characteristics		
Back pain intensity	-	0-10
Leg pain intensity	-	0-10
Constant pain symptoms	Yes	-
Pain described as burning pain	Yes	
Duration of back pain symptoms in current episode	< 6 weeks	-
	6 to 12 weeks	-
	> 3 months	-
Duration of leg pain symptoms in current episode	< 6 weeks	-
	6 to 12 weeks	-
	> 3 months	-
Widespread pain[†]	Yes	-
Leg pain worse than back pain	Yes	-
Pain location	Presence of pain below the knee	-
	Presence of pain in one leg	-

Limitations in activities		
LBLP-related disability (RMDQ)	-	0-23
Pain interference with work (0-10) ‡|	-	0-10
Risk of persistent disability due to back pain (STarT Back)	Low risk	-
	Medium risk	-
	High risk	-
Psychological characteristics and illness perceptions		
HADS (depression)	Normal (0 to 7)	-
	Possible (mild) cases (8 to 10)	-
	Probable (moderate/ severe cases (≥11)	-
HADS (anxiety)	Normal (0 to 7)	-
	Possible (mild) cases (8 to 10)	-
	Probable (moderate/ severe cases (≥11)	-
Pain self-efficacy (PSEQ)§	-	0-60
Illness perceptions (IPQ-R), Timeline "back/leg pain will last for a long time"	Agree or strongly agree	-
Illness perceptions (IPQ-R), Personal control "what I can do determines whether back/leg pain gets better"	Agree or strongly agree	-
Neurological examination findings		

Muscle strength[‖]	5/5	-
	4/5	-
	0/5 or 1/5 or 2/5 or 3/5	-
Presence of either reduced or absent lower limb reflex	None	-
	Slightly reduced	-
	Significantly reduced or absent	-
Sensation to pin-prick in the leg(s)	Normal	-
	Reduction to pin-prick	
	Loss to pin-prick	
Presence of allodynia or hyperalgesia in the leg(s) [**]	Yes	-
Neural tension test [††] (any positive test)	Yes	-
Presence of pins and needles	Yes	-
Pain affects the colour of patients skin	Yes	
Neuroimaging		
Clear or possible nerve root compression	Yes	-
Pain medication [‡‡]		
Number of pain medications	None	-
	One	-
	Two or more	-

Type of pain medication (one or more)	First-line neuropathic pain medication	-
	Basic analgesics	-
	Opioids	-
	NSAID's	-
	Skeletal muscle relaxants	-

Abbreviations: BMI, body mass index. CI, confidence intervals. HADS, Hospital Anxiety and Depression scale. Kg/m2, kilograms per metre^2. IPQ-R, Illness perceptions questionnaire-revised. NSAID, non-steroidal anti-inflammatory drugs. PSEQ, pain self-efficacy questionnaire. RMDQ, Roland Morris Disability Questionnaire leg version.

* Co-morbidities include self-reported history of chest problems, heart problems, raised blood pressure, diabetes, and circulation problems in the leg.

† Widespread pain was defined as pain present above and below the waist, in the right- and left-hand sides of the body and in the axial skeleton.

‡ Applicable to those currently in paid job.

§ Higher scores on PSEQ reflect stronger self-efficacy beliefs

|| Muscle strength was tested according to a 6-point grading scale where;

0. No visible flicker of movement or contraction
1. Flicker of movement
2. Full active movement with gravity counterbalanced
3. Full active movement against gravity but not applied resistance
4. Full active movement against gravity and some applied resistance
5. Full active movement against gravity and strong resistance.

** Hyperalgesia is an increased pain response to painful stimuli. Allodynia is pain response to non-painful stimuli (for example, brush strokes).

†† Neural tension tests; straight leg raise, femoral stretch and slump test.

‡‡ Pain medications include self-reported history of prescribed medications and those purchased over the counter

5.4 Statistical analysis

Point prevalence was estimated for the three definitions of neuropathic pain previously described (s-LANSS score of 12 or greater, clinical diagnosis of sciatica, and clinical diagnosis of sciatica with clear or possible evidence of nerve root compression on MRI). Descriptive statistics (mean and standard deviation (SD) for continuous variables and frequency and percentage for categorical variables) were used to describe characteristics of interest in those with neuropathic pain as defined by each

of the three definitions. Logistic regression was used to examine the association between neuropathic pain (based on the three definitions) and characteristics of interest. The analysis in this chapter is based on complete cases.

5.5 Results

In total, 609 patients with LBLP were eligible and consented to participate in the ATLAS study, all of these patients received a clinical diagnosis of sciatica or referred leg pain and 554 patients had an MRI. Three patients did not complete all seven items of the s-LANSS.

5.5.1 Prevalence of neuropathic pain

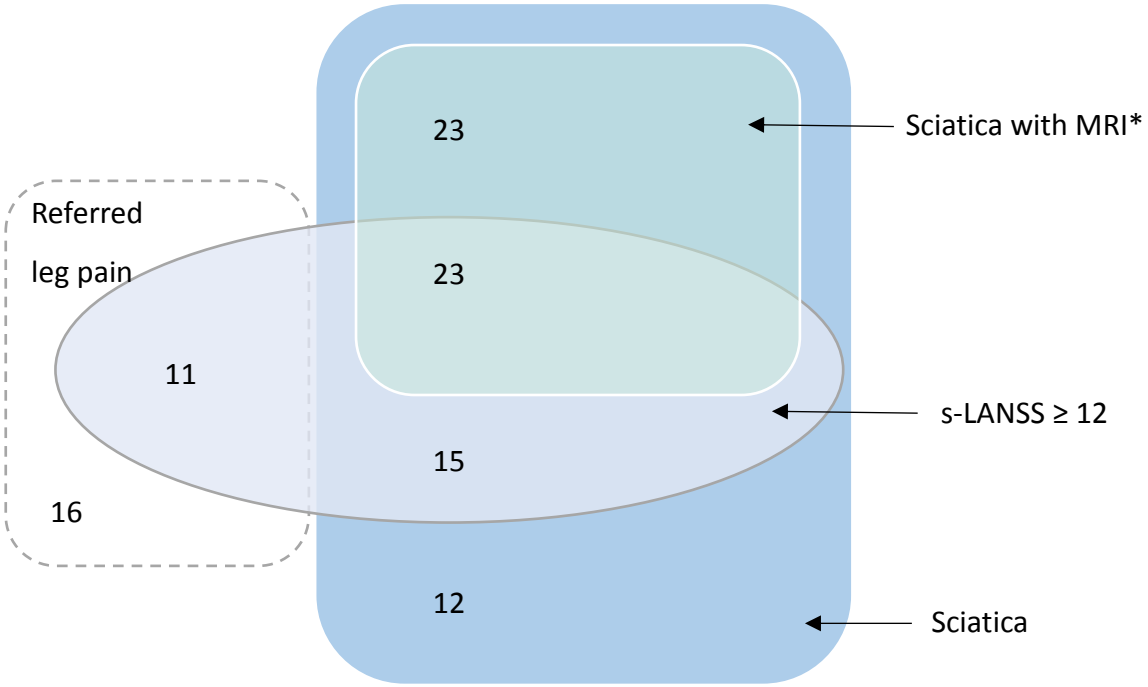
Just under one quarter (23.0%, 127 out of 551) of LBLP patients were defined as having neuropathic pain using all three definitions. Nearly four in ten patients (38.3%, 232 out of 606) were defined as having neuropathic pain based on s-LANSS and clinical diagnosis of sciatica. One in ten (10.7%, 61 out of 606) LBLP patients were defined as having neuropathic pain based on s-LANSS but were not defined as having neuropathic pain by clinical diagnosis of sciatica either with or without evidence of nerve root compression. Table 5.2 presents the estimated prevalence of neuropathic pain in these patients. The distribution and overlap of LBLP patients with or without neuropathic pain based on the three definitions are then summarised in Figure 5.1.

Table 5.2 Prevalence of neuropathic pain in patients based on three definitions

Definition of neuropathic pain	Estimated prevalence
s-LANSS ≥ 12	293 out of 606, 48.4%
Clinical diagnosis of sciatica	452 out of 609, 74.2%
Clinical diagnosis of sciatica with clear or possible evidence of nerve root compression	252 out of 554, 45.5%

Abbreviation: s-LANSS, self-report version of Leeds Assessment of Neurological Symptoms and Signs neuropathic pain scale

Figure 5.1 Venn diagram depicting the overlap between patients with and without neuropathic pain at baseline based on three case definitions



Numbers are percentages of the total in the study
Abbreviations: MRI, magnetic resonance imaging. s-LANSS, self-report version of the Leeds Assessment of Neurological symptoms and signs
*Evidence of clear or possible nerve root compression on MRI

5.5.2 Characteristics of patients with neuropathic pain defined by s-LANSS

5.5.2.1 Sociodemographic characteristics

Over two-thirds (68.3%) of LBLP patients with neuropathic pain were female, and the odds of presenting with neuropathic pain was 1.55 times higher for female patients (odds ratio (OR) 1.55, 95% confidence interval (CI) 1.10 to 2.16). Over half (50.4%) of patients with neuropathic pain were in routine and manual occupations with the odds of presenting with neuropathic pain increasing by 64% for patients in routine and manual occupations compared to those in higher managerial, administrative and professional occupations (OR 1.64, CI 1.07 to 2.50). Patients with neuropathic pain reported not being in paid work more often than those without (65.0% vs 56.4%) but when adjusted for socio-economic status there was no association between not having a paid job and neuropathic pain (OR 1.22, CI 0.87 to 1.73).

5.5.2.2 Health status

LBLP patients with neuropathic pain defined in this way most commonly reported fair general health (39.7%), one in ten (10.6%) patients reported poor general health, the remaining patients reported having excellent, very good or good general health. The odds of presenting with neuropathic pain increased in those patients who reported poor health, fair health and good health compared to those with excellent or very good health. A high proportion of patients with neuropathic pain reported fatigue (74.3%) and difficulties with sleep (88.4%) due to back and leg pain. The odds of presenting with neuropathic pain increased for patients reporting fatigue (OR 1.56, CI

1.10 to 2.23) and for patients reporting difficulty with sleep due to back or leg pain (OR 1.68, CI 1.06 to 2.66).

5.5.2.3 Pain characteristics

The proportion of patients with widespread pain, pain in one leg and with leg pain worse than back pain, were similar between patients with and without neuropathic pain. Back pain and leg pain duration was also similar between the two groups.

Mean (SD) back pain intensity was slightly higher among the patients with neuropathic pain (5.5 (1.6)) compared to those without (5.1 (1.6)). For patients with neuropathic pain mean (SD) leg pain intensity was 5.8 (2.3), with the odds of having neuropathic pain increasing by 20% (OR 1.20, CI 1.12 to 1.29) for every one unit increase in leg pain intensity. Over three-quarters (77.8%) of patients with neuropathic pain reported having pain below the knee. The odds of presenting with neuropathic pain was nearly twice that of patients without pain below the knee (OR 1.98, CI 1.38 to 2.87).

5.5.2.4 Limitations in activities, participation and risk of persistent disabling pain

Patients with neuropathic pain reported LBLP-related disability (RMDQ) mean (SD) score of 13.8 (5.6), for every one-unit increase in disability score, the odds of having neuropathic pain increased by 8% (OR 1.08, CI 1.05 to 1.11).

5.5.2.5 Psychological and illness perception variables

The odds of having neuropathic pain increased in those patients with moderate/severe depressive symptoms (OR 4.14, CI 2.53 to 6.78) and in those with mild symptoms (OR 1.95, CI 1.29 to 2.96) compared to those without depressive symptoms. As regards

anxiety symptoms, the odds of having neuropathic pain increased in those patients with moderate/severe anxiety (OR 3.30, CI 2.22 to 4.87) compared to those without anxiety. There was a significant association between pain self-efficacy and neuropathic pain. LBLP patients with neuropathic pain reported mean (SD) pain self-efficacy score of 30.8 (14.6), for every one-unit reduction in pain self-efficacy, the odds of having neuropathic pain increased by 3% (OR 0.97, CI 0.97 to 0.98).

5.5.2.6 Neurological examination findings

Mild muscle weakness (4 out of 5 on a 0 to 5 grading scale) but not severe muscle weakness (0 to 3 on a 0 to 5 grading scale) was associated with neuropathic pain. Having significantly reduced or absent reflexes was associated with neuropathic pain, but slightly reduced reflexes was not. The odds of presenting with neuropathic pain was associated with either a reduction (OR 1.64, CI 1.16 to 2.33) or loss (OR 2.49, CI 1.35 to 4.60) of pin-prick sensation in the leg(s), pins and needles in the leg(s) (OR 5.8, CI 4.08 to 8.23) and pain that affected the colour of the skin (OR 13.45, CI 5.70 to 31.70).

A small proportion of patients were found to have an increased pain response to either painful or non-painful stimuli on examination (58 out of 609, 9.5%) and the odds of presenting with neuropathic pain was 2.75 times higher for LBLP patients who reported this pain characteristic (CI 1.52 to 4.97). Four out of ten patients (256 out of 609, 42%) self-reported having an increased pain response to either painful or non-painful stimuli (determined from the third item of s-LANSS). Six out of ten (35 out of 58, 60.3%) LBLP patients who self-reported increased pain response to either painful

or non-painful stimuli were found to have the same pain response on clinical examination, suggesting a moderate level of agreement between self-report and clinical examination findings.

5.5.2.7 Neuroimaging

The odds of presenting with neuropathic pain for patients with either clear or possible nerve root compression on MRI were no different compared to those without (OR 0.93, CI 0.66 to 1.30).

5.5.2.8 Pain medication

Patients with neuropathic pain were as likely to report having purchased pain medication over the counter or having been prescribed basic analgesia, first line neuropathic pain medication, non-steroidal anti-inflammatory medication (for example diclofenac sodium or naproxen) and skeletal muscle relaxants (diazepam) for back and leg pain compared to those without. Patients using two or more analgesic medications were more likely to present with neuropathic pain compared to those patients who reported taking no medications (OR 1.83, CI 1.11 to 3.01).

Patients using any opioid were more likely to present with neuropathic pain compared to those not taking any (OR 1.54, CI 1.11 to 2.12). Similar proportions of patients used Co-codamol (a weak to moderate strength opioid) with (34.5%, 101 out of 293) and without neuropathic pain (35.1%, 110 out of 313) but a higher proportion of patients with neuropathic pain used a strong or very strong opioid (one of Buprenorphine, Codeine, Co-dydramol, Nefopam, Dihydrocodeine, Tramadol, Morphine and/or Oxycodone) (23.9%, 70 out of 293) compared to those without (13.4%, 42 out of 313).

Table 5.3 Baseline characteristics of patients with neuropathic pain based on s-LANSS

Characteristics*		**Neuropathic pain (s-LANSS ≥ 12)**		**Unadjusted odds ratio (95% CI)**
		Yes, n=293 (48.4%)	*No, n=313 (51.7%)*	
Sociodemographic characteristics				
Female (n=606)		200 (68.3)	182 (58.2)	1.55 (1.10, 2.16)
Age, mean (SD) (n=606)		49.8 (13.5)	50.4 (14.2)	1.00 (0.99, 1.01)
Socio-economic status (n=590)	Higher managerial, administrative and professional occupations	49 (17.4)	79 (25.7)	1
	Intermediate occupations	71 (25.2)	86 (27.9)	1.33 (0.83, 2.14)
	Routine and manual occupations	142 (50.4)	140 (45.5)	1.64 (1.07, 2.5)
	Never worked and long-term unemployed	20 (7.1)	3 (1.0)	10.75 (3.03, 38.07)
	Never	99 (33.9)	127 (40.6)	1

Characteristics*		**Neuropathic pain (s-LANSS ≥ 12)**		**Unadjusted odds ratio (95% CI)**
		Yes, n=293 (48.4%)	*No, n=313 (51.7%)*	
Smoking status (n=605)	Ex-smoker	80 (27.4)	105 (33.6)	0.98 (0.66, 1.45)
	Current	113 (38.7)	81 (25.9)	1.79 (1.21, 2.64)
BMI (kg/m^2), mean (SD) (n=598)		29.7 (6.1)	29.5 (5.6)	1.01 (0.98, 1.03)
Health status				
Co-morbidities‡, (n=606)	No other health problems	180 (61.4)	190 (60.7)	1
	One other health problem	74 (25.3)	75 (26.8)	0.89 (0.60, 1.31)
	Two or more other health problems	39 (13.3)	31 (11.1)	1.13 (0.66, 1.91)
	Self-reported diabetes	25 (8.5)	22 (7.0)	1.23 (0.68, 2.24)
Self-reported general health (n=605)	Excellent/ very good	52 (17.8)	93 (29.7)	1
	Good	93 (31.9)	78 (24.9)	2.13 (1.35, 3.36)
	Fair	116 (39.7)	123 (39.3)	1.69 (1.10, 2.58)

Characteristics*		Neuropathic pain (s-LANSS ≥ 12)		Unadjusted odds ratio (95% CI)
		Yes, n=293 (48.4%)	*No, n=313 (51.7%)*	
	Poor	31 (10.6)	19 (6.1)	2.92 (1.50, 5.67)
Fatigue (n=593)		214 (74.3)	198 (64.9)	1.56 (1.10, 2.23)
Sleep difficulties (n=601)		258 (88.4)	253 (81.9)	1.68 (1.06, 2.66)
Pain characteristics				
Back pain intensity (0-10), mean (SD) (n=600)		5.5 (1.6)	5.1 (1.6)	1.15 (1.04, 1.27)
Leg pain intensity (0-10) mean (SD), (n=578)		5.8 (2.3)	4.7 (2.4)	1.20 (1.12, 1.29)
Constant pain symptoms (n=594)		221 (75.4)	177 (58.8)	2.15 (1.51, 3.06)
Pain described as burning pain (n=606)		165 (56.3)	55 (17.6)	6.05 (4.18, 8.77)

Characteristics*		Neuropathic pain (s-LANSS ≥ 12)		Unadjusted odds ratio (95% CI)
		Yes, n=293 (48.4%)	*No, n=313 (51.7%)*	
Duration of back pain symptoms in current episode (n=604)	< 6 weeks	98 (33.7)	119 (38.0)	1
	6 to 12 weeks	65 (22.3)	60 (19.2)	1.32 (0.87, 2.04)
	> 3 months	128 (44.0)	134 (42.8)	1.16 (0.81, 1.66)
Duration of leg pain symptoms in current episode (n=580)	< 6 weeks	110 (39.3)	141 (47.0)	1
	6 to 12 weeks	61 (21.8)	58 (19.3)	1.18 (0.75, 1.86)
	> 3 months	109 (38.9)	101 (33.7)	1.41 (0.96, 2.08)
Widespread pain [§] (n=590)		124 (42.9)	125 (41.5)	1.05 (0.74, 1.47)
Leg pain worse (n=604)		138 (47.4)	139 (44.4)	1.13 (0.82, 1.56)
Pain location (n=606)	Pain below the knee	228 (77.8)	200 (63.9)	1.98 (1.38, 2.87)
	Pain in one leg	211 (72.0)	244 (78.0)	0.73 (0.50, 1.06)
Limitations in activities, participation and risk of persistent disabling pain				
LBLP-related disability		13.8 (5.6)	11.5 (5.6)	1.08 (1.05, 1.11)

Characteristics*		Neuropathic pain (s-LANSS ≥ 12)		Unadjusted odds ratio (95% CI)
		Yes, n=293 (48.4%)	*No, n=313 (51.7%)*	
(RMDQ, 0-23), mean (SD) (n=606)				
Pain interference with work (0-10) ǁ (n=360), mean (SD)		6.3 (3.0)	5.4 (3.0)	1.11 (1.03, 1.20)
Risk of persistent disability due to back pain (STarT Back) (n=530)	Low risk	29 (10.2)	53 (17.6)	1
	Medium risk	120 (42.3)	154 (51.0)	1.57 (0.92, 2.7)
	High risk	135 (47.5)	95 (31.5)	2.7 (1.56, 4.7)
Psychological characteristics and illness perceptions				
Depression (HADS) (n=606)	Normal (0 to 7)	155 (52.9)	235 (75.1)	1
	Possible (mild) cases (8 to 10)	67 (22.9)	52 (16.6)	1.95 (1.29, 2.96)
	Probable (moderate/severe) cases (≥11)	71 (24.2)	26 (8.3)	4.14 (2.53, 6.78)
	Normal (0 to 7)	118 (40.6)	196 (62.6)	1

Characteristics*		Neuropathic pain (s-LANSS ≥ 12)		Unadjusted odds ratio (95% CI)
		Yes, n=293 (48.4%)	*No, n=313 (51.7%)*	
Anxiety (HADS) (n=604)	Possible (mild) cases (8 to 10)	60 (20.6)	60 (19.2)	1.66 (1.08, 2.54)
	Probable (moderate/ severe) cases (≥11)	113 (38.8)	57 (18.2)	3.30 (2.22, 4.87)
Pain self-efficacy (PSEQ, 0-60)† (n=590), mean (SD)		30.8 (14.6)	37.4 (13.8)	0.97 (0.96, 0.98)
Illness perceptions (IPQ-R)	Timeline "back/leg pain will last for a long time" (agree or strongly agree) (n=602)	175 (59.7)	169 (54.0)	1.26 (0.92, 1.74)
	Personal control "what I can do determines whether	104 (35.9)	118 (37.8)	0.92 (0.66, 1.28)

Characteristics*		Neuropathic pain (s-LANSS ≥ 12)		Unadjusted odds ratio (95% CI)
		Yes, n=293 (48.4%)	*No, n=313 (51.7%)*	
	back/leg pain gets better" (agree or strongly agree) (n=606)			
Neurological examination findings				
Muscle weakness** **(n=606)**	5/5	231 (78.8)	270 (86.3)	1
	4/5	56 (19.1)	36 (11.5)	1.81 (1.15, 2.86)
	0 to 3/5	6 (2.1)	7 (2.2)	1.00 (0.33, 3.02)
Reflex change (n=606)	None	222 (75.8)	265 (84.7)	1
	Slightly reduced	19 (6.5)	11 (3.5)	2.06 (0.96, 4.43)
	Significantly reduced or absent	52 (17.8)	37 (11.8)	1.68 (1.06, 2.65)
Sensation to pin-prick in the leg(s) (n=606)	Normal	150 (51.2)	204 (65.2)	1
	Reduction to pin-prick	110 (37.5)	91 (29.1)	1.64 (1.16, 2.33)
	Loss to pin-prick	33 (11.3)	18 (5.8)	2.49 (1.35, 4.60)

Characteristics*	Neuropathic pain (s-LANSS ≥ 12)		Unadjusted odds ratio (95% CI)
	Yes, n=293 (48.4%)	*No, n=313 (51.7%)*	
Presence of allodynia or hyperalgesia in the leg(s)[§§] (n=606)	40 (13.7)	17 (5.4)	2.75 (1.52, 4.97)
Neural tension test[‡‡] (any positive test, n=606)	168 (57.3)	165 (52.7)	1.21 (0.87, 1.66)
Pins and needles in the leg(s) (n=606)	209 (71.3)	84 (28.7)	5.80 (4.08, 8.23)
Pain affects the colour of patients skin (n=606)	61 (20.8)	6 (1.9)	13.45 (5.70, 31.7)
Neuroimaging			
Clear or possible nerve root compression (n=551)	142 (52.8)	154 (54.6)	0.93 (0.66, 1.30)

Characteristics*		Neuropathic pain (s-LANSS ≥ 12)		Unadjusted odds ratio (95% CI)
		Yes, n=293 (48.4%)	*No, n=313 (51.7%)*	
Pain medications [§§] (n=606)				
Number of pain medications	None	34 (11.6)	49 (15.7)	1
	One	103 (35.2)	141 (45.1)	1.05 (0.63, 1.75)
	Two or more	156 (53.2)	123 (39.3)	1.83 (1.11, 3.01)
Type of pain medication (one or more)	First-line neuropathic pain medication	35 (12.0)	32 (10.2)	1.19 (0.72, 1.98)
	Basic analgesics	147 (50.2)	142 (45.4)	1.21 (0.88, 1.67)
	Opioids	178 (60.8)	157 (50.2)	1.54 (1.11, 2.12)
	NSAID's	49 (16.7)	46 (14.7)	0.17 (0.75, 1.81)
	Skeletal muscle relaxants	8 (2.7)	5 (1.6)	1.73 (0.56, 5.35)

Figures are frequencies (percentages) unless stated otherwise as mean (SD).
Odds ratio (confidence intervals) underlined highlights characteristics associated with neuropathic pain.
Abbreviations: BMI, body mass index. CI, confidence intervals. HADS, Hospital Anxiety and Depression scale. Kg/m2, kilograms per metre^2. IPQ-R, Illness perceptions questionnaire-revised. NSAID, non-steroidal anti-inflammatory drugs. PSEQ, pain self-efficacy questionnaire. RMDQ, Roland Morris Disability Questionnaire leg version. SD, standard deviation. S-LANSS, self-report version of Leeds Assessment for Neurological Symptoms and Signs neuropathic pain scale.
*Denominator varies for some characteristics due to missing data or not applicable case.
† Higher scores on PSEQ reflect stronger self-efficacy beliefs
‡ Co-morbidities include self-reported history of chest problems, heart problems, raised blood pressure, diabetes, and circulation problems in the leg.
§ Widespread pain was defined as pain present above and below the waist, in the right- and left-hand sides of the body and in the axial skeleton.
|| Applicable to those currently in paid job.

** Muscle strength was tested according to a 6-point grading scale where;

0. No visible flicker of movement or contraction
1. Flicker of movement
2. Full active movement with gravity counterbalanced
3. Full active movement against gravity but not applied resistance
4. Full active movement against gravity and some applied resistance
5. Full active movement against gravity and strong resistance.

§§ Hyperalgesia is an increased pain response to painful stimuli. Allodynia is pain response to non-painful stimuli (for example, brush strokes).

‡‡ Neural tension tests; straight leg raise, femoral stretch and slump test.

[§§] Pain medications include self-reported history of prescribed medications and those purchased over the counter

5.5.3 Characteristics of patients with neuropathic pain based on a clinical diagnosis of sciatica

There were no significant differences in characteristics that described health status and pain medication use between patients with and without neuropathic pain. LBLP patients with neuropathic pain reported higher mean (SD) leg pain intensity compared to those without (5.6 (2.3) vs. 4.2 (2.2)). For every one-unit increase in NRS score for leg pain intensity, the unadjusted odds of presenting with neuropathic pain increased by 32% (OR 1.32, CI 1.21 to 1.44). There was a significant association between neuropathic pain and pain self-efficacy. LBLP patients with a clinical diagnosis of neuropathic pain reported mean (SD) pain self-efficacy (PSEQ) 33.3 (14.7), for every one-unit reduction in PSEQ the odds of having neuropathic pain (sciatica) increased by 2% (OR 0.98, CI 0.97 to 1.00). Characteristics describing pain location and characteristics of the neurological examination were strongly associated with neuropathic pain. LBLP patients with either clear or possible nerve root compression on MRI were over 3 times more likely to have neuropathic pain compared to those without (OR 3.23, CI 2.15 to 4.85).

Table 5.4 Baseline characteristics of patients with neuropathic pain defined by clinical diagnosis of sciatica

Characteristics*		**Neuropathic pain (Clinical diagnosis of sciatica)**		**Unadjusted odds ratio (95% CI)**
		Yes, n=452 (74.2%)	*No, n=157 (25.8%)*	
Sociodemographic characteristics				
Female (n=609)		277 (61.3)	106 (67.52)	0.76 (0.52, 1.12)
Age, mean (SD) (n=609)		50.4 (14.0)	49.5 (13.7)	1.01 (0.99, 1.02)
Socio-economic status (n=593)	Higher managerial, administrative and professional occupations	89 (20.3)	40 (25.8)	1
	Intermediate occupations	120 (27.4)	38 (24.5)	1.42 (0.84, 2.39)
	Routine and manual occupations	210 (48.0)	73 (47.1)	1.29 (0.82, 2.04)
	Never worked and long-term unemployed	18 (4.3)	4 (2.6)	2.13 (1.68, 6.68)
Smoking status (n=608)	Never	169 (37.5)	58 (36.9)	1
	Ex-smoker	131 (29.1)	56 (35.7)	0.80 (0.52, 1.24)

Characteristics*		Neuropathic pain (Clinical diagnosis of sciatica)		Unadjusted odds ratio (95% CI)
		Yes, n=452 (74.2%)	*No, n=157 (25.8%)*	
	Current	151 (33.5)	43 (27.4)	1.21 (0.77, 1.89)
BMI (kg/m^2), mean (SD) (n=601)		29.8 (6.0)	29.1 (5.6)	1.02 (0.99, 1.05)
Health status				
Co-morbidities ‡, (n=608)	No other health problems	277 (61.3)	94 (59.9)	1
	One other health problem	122 (27.0)	36 (22.9)	1.15 (0.74, 1.78)
	Two or more other health problems	53 (11.7)	27 (17.2)	0.67 (0.40, 1.12)
	Self-reported diabetes	37 (8.2)	11 (7.0)	1.18 (0.59, 2.38)
Self-reported general health (n=608)	Excellent/ very good	111 (24.6)	35 (22.3)	1
	Good	124 (27.5)	48 (30.6)	0.81 (0.49, 1.35)
	Fair	177 (39.3)	63 (40.1)	0.89 (0.55, 1.43)
	Poor	39 (8.7)	11 (7.0)	1.12 (0.52, 2.41)
Fatigue (n=593)		214 (74.3)	198 (64.9)	1.18 (0.79, 1.78)

Characteristics*		Neuropathic pain (Clinical diagnosis of sciatica)		Unadjusted odds ratio (95% CI)
		Yes, n=452 (74.2%)	*No, n=157 (25.8%)*	
Sleep difficulties (n=604)		385 (85.8)	129 (83.2)	0.82 (0.50, 1.36)
Pain characteristics				
Back pain intensity (0-10), mean (SD) (n=603)		5.3 (1.6)	5.3 (1.6)	0.98 (0.87, 1.09)
Leg pain intensity (0-10), mean (SD) (n=581)		5.6 (2.3)	4.2 (2.2)	1.32 (1.21, 1.44)
Constant pain symptoms (n=597)		305 (68.7)	96 (62.8)	1.30 (0.89, 1.91)
Pain described as burning pain (n=609)		166 (36.7)	55 (35.0)	1.08 (0.74. 1.57)
Duration of back pain symptoms in current episode (n=607)	< 6 weeks	174 (38.6)	44 (28.2)	1
	6 to 12 weeks	96 (21.3)	30 (19.2)	0.81 (0.48, 1.37)
	> 3 months	181 (40.1)	82 (52.6)	0.59 (0.37, 0.85)
	< 6 weeks	192 (44.2)	59 (39.6)	1

Characteristics*		Neuropathic pain (Clinical diagnosis of sciatica)		Unadjusted odds ratio (95% CI)
		Yes, n=452 (74.2%)	*No, n=157 (25.8%)*	
Duration of leg pain symptoms in current episode (n=583)	6 to 12 weeks	94 (21.7)	26 (17.5)	1.11 (0.66, 1.87)
	> 3 months	148 (34.1)	64 (43.0)	0.71 (0.47, 1.07)
Widespread pain [§] (n=592)		171 (38.8)	79 (52.3)	0.58 (0.40, 0.84)
Leg pain worse (n=607)		251 (55.8)	28 (17.8)	5.81 (3.71, 9.10)
Pain location (n=609)	Pain below the knee	375 (83.0)	55 (35.0)	9.03 (6.00, 13.60)
	Pain in one leg	368 (81.4)	89 (56.7)	3.35 (2.26, 4.97)
Limitations in activities, participation and risk of persistent disabling pain				
LBLP-related disability (RMDQ) (0-23), mean (SD) (n=609)		12.9 (5.7)	11.9 (5.7)	1.03 (0.997, 1.06)
Pain interference with work (0-10) [‖] (n=361), mean (SD)		6.0 (2.9)	5.4 (2.8)	1.08 (0.99, 1.17)

Characteristics*		Neuropathic pain (Clinical diagnosis of sciatica)		Unadjusted odds ratio (95% CI)
		Yes, n=452 (74.2%)	*No, n=157 (25.8%)*	
Risk of persistent disabling pain (STarT Back) (n=589)	Low risk	53 (12.1)	29 (19.1)	1
	Medium risk	212 (48.5)	64 (42.1)	1.81 (1.06, 3.09)
	High risk	172 (39.4)	59 (38.8)	1.60 (0.93, 2.74)
Psychological characteristics and illness perceptions				
Depression (HADS) (n=609)	Normal (0 to 7)	295 (65.3)	97 (61.8)	1
	Possible (mild) cases (8 to 10)	82 (18.1)	37 (23.6)	0.73 (0.46, 1.14)
	Probable (moderate/severe) cases (≥11)	75 (16.6)	23 (14.7)	1.07 (0.64, 1.80)
Anxiety (HADS) (n=607)	Normal (0 to 7)	249 (55.2)	67 (43.0)	1
	Possible (mild) cases (8 to 10)	86 (19.1)	34 (21.8)	0.68 (0.42, 1.10)
	Probable (moderate/ severe) cases (≥11)	116 (25.7)	55 (35.3)	0.57 (0.37, 0.86)
Pain self-efficacy (PSEQ, 0-60)†		33.3 (14.7)	36.6 (13.9)	0.98 (0.97, 0.997)

Characteristics*		Neuropathic pain (Clinical diagnosis of sciatica)		Unadjusted odds ratio (95% CI)
		Yes, n=452 (74.2%)	*No, n=157 (25.8%)*	
(n=593), mean (SD)				
Illness perceptions (IPQ-R)	Timeline "back/leg pain will last for a long time" (agree or strongly agree) (n=605)	249 (55.1)	96 (61.5)	0.78 (0.54, 1.13)
	Personal control "what I can do determines whether back/leg pain gets better" (agree or strongly agree) (n=609)	162 (36.2)	62 (36.2)	0.87 (0.60, 1.27)
Neurological examination findings				
Muscle weakness ** **(n=608)**	5/5	347 (76.8)	156 (100.0)	1
	4/5	92 (20.4)	0 (0.00)	-
	0 to 3/5	13 (2.9)	0 (0.00)	-

Characteristics*		Neuropathic pain (Clinical diagnosis of sciatica)		Unadjusted odds ratio (95% CI)
		Yes, n=452 (74.2%)	*No, n=157 (25.8%)*	
Reflex change (n=609)	None	341 (75.4)	149 (94.9)	1
	Slightly reduced	30 (6.6)	0 (0.00)	-
	Significantly reduced or absent	81 (17.9)	8 (5.1)	4.42 (2.09, 9.38)
Sensation to pin-prick in the leg(s) (n=609)	Normal	226 (50.0)	130 (82.8)	1
	Reduction to pin-prick	175 (38.7)	26 (16.6)	3.87 (2.43, 6.16)
	Loss to pin-prick	51 (11.3)	1 (0.64)	29.33 (4.01, 214.78)
Presence of allodynia or hyperalgesia in the leg(s)[§§] (n=609)		47 (10.4)	11 (7.0)	1.54 (0.78, 3.05)
Neural tension test[‡‡] (any positive test, n=609)		324 (71.7)	11 (7.0)	33.60 (17.61, 64.10)

Characteristics*		Neuropathic pain (Clinical diagnosis of sciatica)		Unadjusted odds ratio (95% CI)
		Yes, n=452 (74.2%)	*No, n=157 (25.8%)*	
Pins and needles in the leg(s) (n=609)		256 (56.6)	49 (31.2)	2.88 (1.96, 4.23)
Pain affects the colour of patients skin (n=609)		51 (11.3)	16 (10.3)	1.12 (0.62, 2.03)
Neuroimaging				
Clear or possible nerve root compression (n=554)		252 (60.7)	45 (32.4)	3.23 (2.15, 4.85)
Pain medication§§ (n=609)				
Number of pain medications	None	61 (13.5)	23 (14.7)	1
	One	177 (39.2)	69 (44.0)	0.97 (0.56, 1.68)
	Two or more	214 (47.4)	65 (41.4)	1.24 (0.71, 2.16)
Type of pain medication	First-line neuropathic pain medication	54 (12.0)	13 (8.3)	1.50 (0.80, 2.84)
	Basic analgesics	216 (47.8)	73 (46.5)	1.05 (0.73, 1.52)
	Opioids	260 (57.5)	77 (49.0)	1.42 (0.98, 2.03)

Characteristics*		Neuropathic pain (Clinical diagnosis of sciatica)		Unadjusted odds ratio (95% CI)
		Yes, n=452 (74.2%)	*No, n=157 (25.8%)*	
	NSAID's	68 (15.0)	27 (17.2)	0.85 (0.52, 1.39)
	Skeletal muscle relaxants	11 (2.4)	2 (1.5)	1.93 (0.42, 8.82)

Figures are frequencies (percentages) unless stated otherwise as mean (SD)
Odds ratio (confidence intervals) underlined highlights characteristics associated with neuropathic pain.
Abbreviations: BMI, body mass index. CI, confidence intervals. HADS, Hospital Anxiety and Depression scale. Kg/m2, kilograms per metre^2. IPQ-R, Illness perceptions questionnaire-revised. NSAID, non-steroidal anti-inflammatory drugs. PSEQ, pain self-efficacy questionnaire. RMDQ, Roland Morris Disability Questionnaire leg version. SD, standard deviation.
*Denominator varies for some characteristics due to missing data or not applicable case.
† Higher scores on PSEQ reflect stronger self-efficacy beliefs
‡ Co-morbidities include self-reported history of chest problems, heart problems, raised blood pressure, diabetes, and circulation problems in the leg.
§ Widespread pain was defined as pain present above and below the waist, in the right- and left-hand sides of the body and in the axial skeleton.
|| Applicable to those currently in paid job.
** Muscle strength was tested according to a 6-point grading scale where;

0. No visible flicker of movement or contraction
1. Flicker of movement
2. Full active movement with gravity counterbalanced
3. Full active movement against gravity but not applied resistance
4. Full active movement against gravity and some applied resistance
5. Full active movement against gravity and strong resistance.

§§ Hyperalgesia is an increased pain response to painful stimuli. Allodynia is pain response to non-painful stimuli (for example, brush strokes).
‡‡ Neural tension tests; straight leg raise, femoral stretch and slump test.
§§ Pain medications include self-reported history of prescribed medications and those purchased over the counter

5.5.4 Characteristics of patients with neuropathic pain based on a clinical diagnosis plus evidence of possible or clear nerve root compression on MRI

The odds of having a clinical diagnosis of neuropathic pain (with evidence of nerve root compression) was 50% less for female patients (OR 0.50, CI 0.35 to 0.70). The mean age (SD) of patients with neuropathic pain was 51.9 (13.1) years and for every one-year increase in age the odds of having neuropathic pain increased by 2% (OR 1.02, CI 1.01 to 1.03).

More severe leg pain intensity was associated with neuropathic pain, for every one-unit increase in NRS score for leg pain intensity, the odds of having neuropathic pain (sciatica with nerve root compression) increased by 29% (OR 1.29, CI 1.19 to 1.40). Patients with neuropathic pain reported more severe LBLP-related disability (RMDQ) mean score (SD) of 13.3 (5.3), for every one-unit increase in the RMDQ score, the odds of having neuropathic pain increased by 4% (OR 1.04, CI 1.02 to 1.08). Patients with moderate/severe depressive symptoms were 1.80 times more likely to present with neuropathic pain compared to those without these symptoms (OR 1.80, CI 1.13 to 2.87). LBLP patients with a clinical diagnosis of neuropathic pain with evidence of nerve root compression reported lower pain self-efficacy scores compared to those without (mean (SD) PSEQ 32.2 (14.6) vs. 36.6 (14.1)). Characteristics that described pain location and characteristics of the neurological examination were strongly associated with neuropathic pain.

Table 5.5 Baseline characteristics of patients with neuropathic pain based on a clinical diagnosis of sciatica and evidence of nerve root compression on MRI

Characteristics*		**Neuropathic pain (Clinical diagnosis of sciatica with clear or possible evidence of nerve root compression)**		**Unadjusted odds ratio (95% CI)**
		Yes, n=252 (45.5%)	*No, n=302 (54.5%)*	
Sociodemographic characteristics				
Female (n=554)		137 (54.4)	213 (70.5)	0.50 (0.35, 0.70)
Age, mean (SD) (n=554)		51.9 (13.1)	48.5 (14.2)	1.02 (1.01, 1.03)
Socio-economic status (n=540)	Higher managerial, administrative and professional occupations	53 (21.7)	70 (23.7)	1
	Intermediate occupations	65 (26.6)	81 (27.4)	1.06 (0.65, 1.72)
	Routine and manual occupations	118 (48.4)	134 (45.3)	1.16 (0.75, 1.80)

Characteristics*		Neuropathic pain (Clinical diagnosis of sciatica with clear or possible evidence of nerve root compression)		Unadjusted odds ratio (95% CI)
		Yes, n=252 (45.5%)	*No, n=302 (54.5%)*	
	Never worked and long-term unemployed	8 (3.3)	11 (3.7)	0.96 (0.36, 2.56)
Smoking status (n=553)	Never	93 (36.9)	110 (36.5)	1
	Ex-smoker	76 (30.2)	93 (30.9)	0.97 (0.64, 1.46)
	Current	83 (32.9)	98 (32.6)	1.00 (0.67, 1.50)
BMI (kg/m^2), mean (SD) (n=549)		29.8 (5.9)	29.1 (5.6)	1.02 (0.99, 1.05)
Health status				
Co-morbidities‡, (n=554)	No other health problems	157 (62.3)	187 (61.9)	1
	One other health problem	67 (26.6)	76 (25.2)	1.05 (0.71, 1.55)
	Two or more other health problems	28 (11.1)	39 (12.9)	0.86 (0.50, 1.45)

Characteristics*		Neuropathic pain (Clinical diagnosis of sciatica with clear or possible evidence of nerve root compression)		Unadjusted odds ratio (95% CI)
		Yes, n=252 (45.5%)	*No, n=302 (54.5%)*	
	Self-reported diabetes	20 (7.9)	22 (7.3)	1.10 (0.58, 2.06)
Self-reported general health (n=553)	Excellent/ very good	65 (25.9)	67 (22.0)	1
	Good	66 (26.3)	90 (29.8)	0.76 (0.47, 1.20)
	Fair	100 (39.8)	122 (40.4)	0.84 (0.55, 1.30)
	Poor	20 (8.0)	23 (7.6)	0.90 (0.45, 1.79)
Fatigue (n=543)		171 (69.5)	209 (70.4)	1.04 (0.72, 1.51)
Sleep difficulties (n=549)		211 (84.4)	253 (84.6)	1.02 (0.64, 1.62)
Pain characteristics				
Back pain intensity (0-10), mean (SD) (n=543)		5.3 (1.7)	5.3 (1.6)	0.99 (0.89, 1.10)
Leg pain intensity (0-10)		6.0 (2.3)	4.6 (2.3)	1.29 (1.19, 1.40)

Characteristics*		Neuropathic pain (Clinical diagnosis of sciatica with clear or possible evidence of nerve root compression)		Unadjusted odds ratio (95% CI)
		Yes, n=252 (45.5%)	*No, n=302 (54.5%)*	
mean (SD), (n=542)				
Constant pain symptoms (n=542)		173 (70.0)	202 (68.5)	1.08 (0.75, 1.55)
Pain described as burning pain (n=554)		87 (34.5)	112 (37.1)	0.89 (0.63, 1.27)
Duration of back pain symptoms in current episode (n=552)	Less than 6 weeks	97 (38.5)	97 (32.3)	1
	6 to 12 weeks	58 (23.0)	58 (19.3)	1.00 (0.63, 1.58)
	> 3 months	97 (38.5)	145 (48.3)	0.67 (0.46, 0.98)
Duration of leg pain symptoms in current episode (n=530)	Less than 6 weeks	106 (43.8)	121 (42.0)	1
	6 to 12 weeks	57 (23.6)	54 (18.8)	1.20 (0.76, 1.90)
	> 3 months	79 (32.6)	113 (39.2)	0.80 (0.54, 1.18)
Widespread pain § (n=540)		71 (28.6)	156 (53.4)	0.35 (0.24, 0.50)

Characteristics*		Neuropathic pain (Clinical diagnosis of sciatica with clear or possible evidence of nerve root compression)		Unadjusted odds ratio (95% CI)
		Yes, n=252 (45.5%)	*No, n=302 (54.5%)*	
Leg pain worse (n=552)		166 (66.1)	88 (29.2)	4.73 (3.30, 6.77)
Pain location (n=554)	Pain below the knee	216 (85.7)	178 (58.9)	4.18 (2.74, 6.37)
	Pain in one leg	210 (83.3)	205 (67.9)	2.37 (1.57, 3.56)
Limitations in activities, participation and risk of persistent disabling pain				
LBLP-related disability (RMDQ, 0-23), mean (SD) (n=554)		13.3 (5.3)	11.9 (5.9)	1.04 (1.02, 1.08)
Pain interference with work (0-10) [ll] (n=333), mean (SD)		6.3 (2.8)	5.5 (3.0)	1.10 (1.02, 1.19)
Risk of persistent disability due to back pain (STarT back) (n=530)	Low risk	27 (11.2)	48 (16.3)	1
	Medium risk	116 (48.1)	139 (47.1)	1.48 (0.87, 2.53)
	High risk	98 (40.7)	108 (36.6)	1.61 (0.94, 2.78)

Characteristics*		Neuropathic pain (Clinical diagnosis of sciatica with clear or possible evidence of nerve root compression)		Unadjusted odds ratio (95% CI)
		Yes, n=252 (45.5%)	*No, n=302 (54.5%)*	
Psychological characteristics and illness perceptions				
Depression (HADS) (n=554)	Normal (0 to 7)	155 (61.5)	200 (66.2)	1
	Possible (mild) cases (8 to 10)	44 (17.5)	64 (21.2)	0.89 (0.57, 1.37)
	Probable (moderate/severe) cases (≥11)	53 (21.0)	38 (12.6)	1.80 (1.13, 2.87)
Anxiety (HADS) (n=553)	Normal (0 to 7)	137 (54.6)	149 (49.3)	1
	Possible (mild) cases (8 to 10)	50 (19.9)	62 (20.5)	0.88 (0.57, 1.36)
	Probable (moderate/ severe) cases (≥11)	64 (25.5)	91 (30.1)	0.76 (0.52, 1.14)
Pain self-efficacy (PSEQ, 0-60)† (n=542), mean (SD)		32.2 (14.6)	36.1 (14.1)	0.98 (0.97, 0.99)

Characteristics*		**Neuropathic pain (Clinical diagnosis of sciatica with clear or possible evidence of nerve root compression)**		**Unadjusted odds ratio (95% CI)**
		Yes, n=252 (45.5%)	*No, n=302 (54.5%)*	
Illness perceptions (IPQ-R)	Timeline "back/leg pain will last for a long time" (agree or strongly agree) (n=554)	133 (52.8)	181 (59.9)	0.75 (0.53, 1.05)
	Personal control "what I can do determines whether back/leg pain gets better" (agree or strongly agree) (n=551)	92 (36.8)	105 (34.9)	1.09 (0.77, 1.54)
Neurological examination findings				
Muscle weakness ** (n=553)	5/5	191 (75.8)	270 (89.7)	1
	4/5	50 (19.8)	31 (10.3)	2.28 (1.40, 3.70)
	0 to 3/5	11 (4.4)	0 (0.0)	-

Characteristics*		Neuropathic pain (Clinical diagnosis of sciatica with clear or possible evidence of nerve root compression)		Unadjusted odds ratio (95% CI)
		Yes, n=252 (45.5%)	*No, n=302 (54.5%)*	
Reflex change (n=554)	None	169 (67.1)	281 (93.1)	1
	Slightly reduced	22 (8.7)	3 (1.0)	12.19 (3.60, 41.4)
	Significantly reduced or absent	61 (24.2)	18 (6.0)	5.63 (3.22, 9.86)
Sensation to pin-prick in the leg(s) (n=554)	Normal	125 (49.6)	199 (65.9)	1
	Reduction to pin-prick	95 (37.7)	86 (28.5)	1.76 (1.22, 2.54)
	Loss to pin-prick	32 (12.7)	17 (5.6)	3.00 (1.60, 5.62)
Presence of allodynia or hyperalgesia in the leg(s)[§§] (n=554)		24 (9.5)	30 (9.9)	0.95 (0.54, 1.68)
Neural tension test[‡‡] (any positive test, n=554)		185 (73.4)	122 (40.4)	4.07 (2.84, 5.85)

Characteristics*		Neuropathic pain (Clinical diagnosis of sciatica with clear or possible evidence of nerve root compression)		Unadjusted odds ratio (95% CI)
		Yes, n=252 (45.5%)	*No, n=302 (54.5%)*	
Pins and needles in the leg(s) (n=554)		137 (54.4)	140 (46.4)	1.38 (0.99, 1.93)
Pain affects the colour of patients skin (n=554)		28 (11.2)	28 (9.3)	1.22 (0.70, 2.12)
Pain medication[§§] (n=554)				
Number of pain medications	None	32 (12.7)	37 (12.3)	1
	One	97 (38.5)	124 (41.1)	0.90 (0.53, 1.56)
	Two or more	123 (48.8)	141 (46.7)	1.01 (0.59, 1.72)
Type of pain medication (one or more)	First-line Neuropathic pain medication	33 (13.1)	28 (9.3)	1.47 (0.86, 2.52)
	Basic analgesics	113 (44.8)	154 (51.0)	0.78 (0.56, 1.09)
	Opioids	151 (59.9)	165 (54.6)	1.24 (0.88, 1.74)
	NSAID's	46 (18.3)	40 (13.3)	1.46 (0.92, 2.32)

Characteristics*		Neuropathic pain (Clinical diagnosis of sciatica with clear or possible evidence of nerve root compression)		Unadjusted odds ratio (95% CI)
		Yes, n=252 (45.5%)	*No, n=302 (54.5%)*	
	Skeletal muscle relaxants	8 (3.2)	5 (1.7)	1.95 (0.63, 6.03)

Figures are frequencies (percentages) unless stated otherwise as mean (SD)
Odds ratio (confidence intervals) underlined highlights characteristics associated with neuropathic pain.
Abbreviations: BMI, body mass index. CI, confidence intervals. HADS, Hospital Anxiety and Depression scale. Kg/m2, kilograms per metre^2. IPQ-R, Illness perceptions questionnaire-revised. NSAID, non-steroidal anti-inflammatory drugs. PSEQ, pain self-efficacy questionnaire. RMDQ, Roland Morris Disability Questionnaire leg version. SD, standard deviation.
*Denominator varies for some characteristics due to missing data or not applicable case.
† Higher scores on PSEQ reflect stronger self-efficacy beliefs
‡ Co-morbidities include self-reported history of chest problems, heart problems, raised blood pressure, diabetes, and circulation problems in the leg.
§ Widespread pain was defined as pain present above and below the waist, in the right- and left-hand sides of the body and in the axial skeleton.
|| Applicable to those currently in paid job.
** Muscle strength was tested according to a 6-point grading scale where;

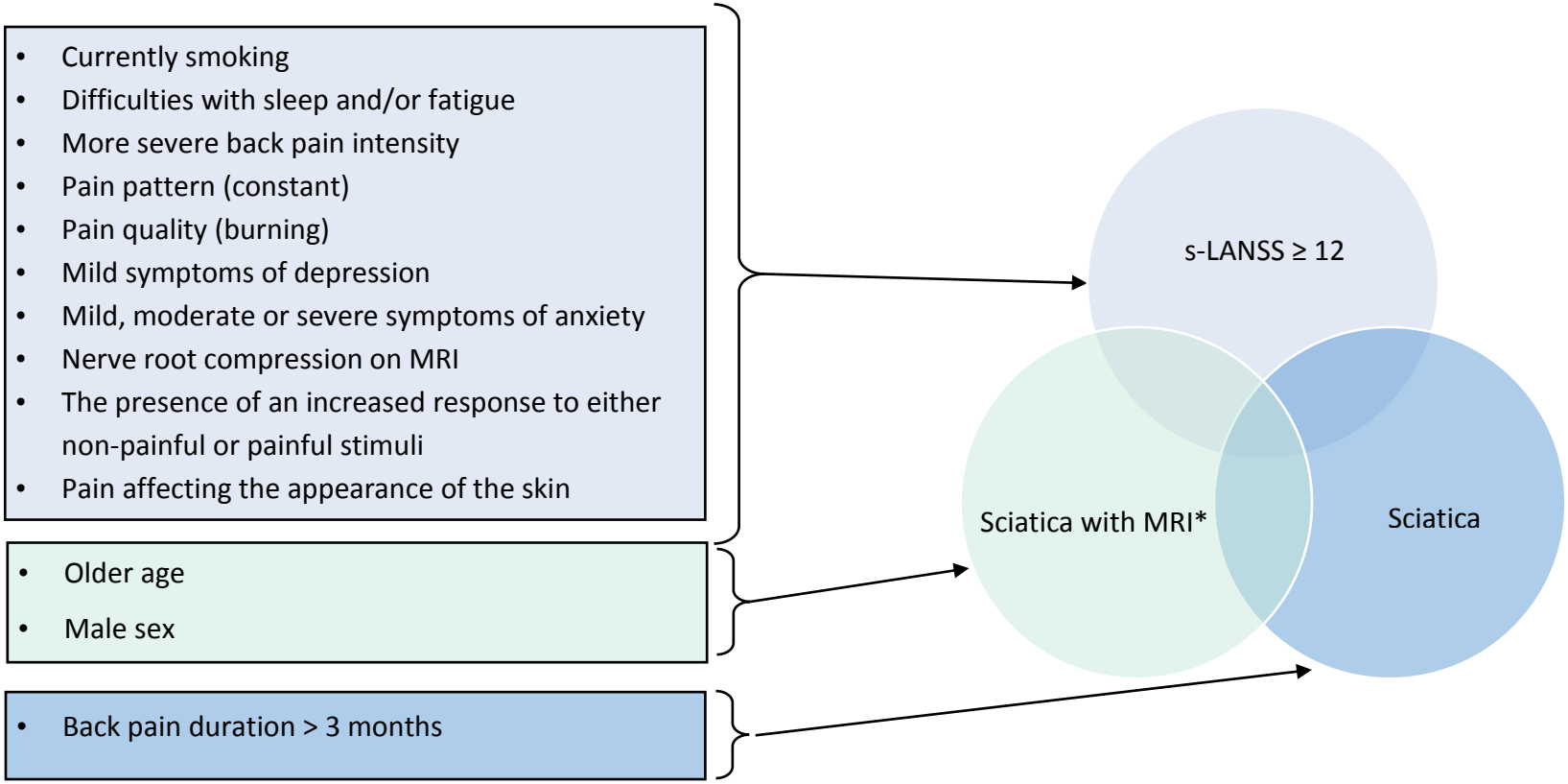
0. No visible flicker of movement or contraction
1. Flicker of movement
2. Full active movement with gravity counterbalanced
3. Full active movement against gravity but not applied resistance
4. Full active movement against gravity and some applied resistance
5. Full active movement against gravity and strong resistance.

§§ Hyperalgesia is an increased pain response to painful stimuli. Allodynia is pain response to non-painful stimuli (for example, brush strokes).
‡‡ Neural tension tests; straight leg raise, femoral stretch and slump test.
§§ Pain medications include self-reported history of prescribed medications and those purchased over the counter

5.5.5 Characteristics of patients with neuropathic pain across three definitions

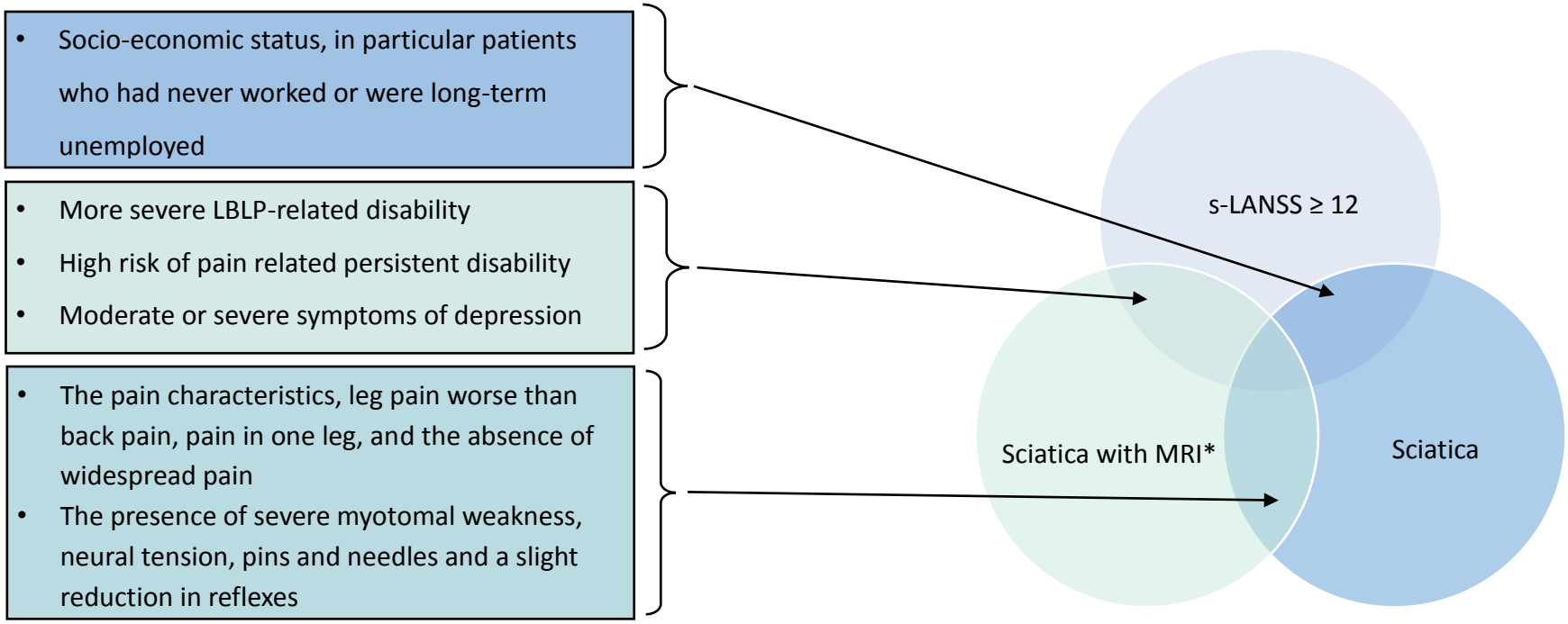
Figures 5.2 to 5.5 summarise the overlap and distribution of characteristics that are described in this research and are associated with neuropathic pain. Figure 5.4 summarises the characteristics that were consistently similar or different in LBLP patients with neuropathic pain compared to those without, across all three definitions. Figure 5.5 summarises pain medication history reported by patients with and without neuropathic pain and includes a summary (Figure 5.5b) of the most common pain medication used, as reported by patients with neuropathic pain.

Figure 5.2 Characteristic associated with only one definition of neuropathic pain



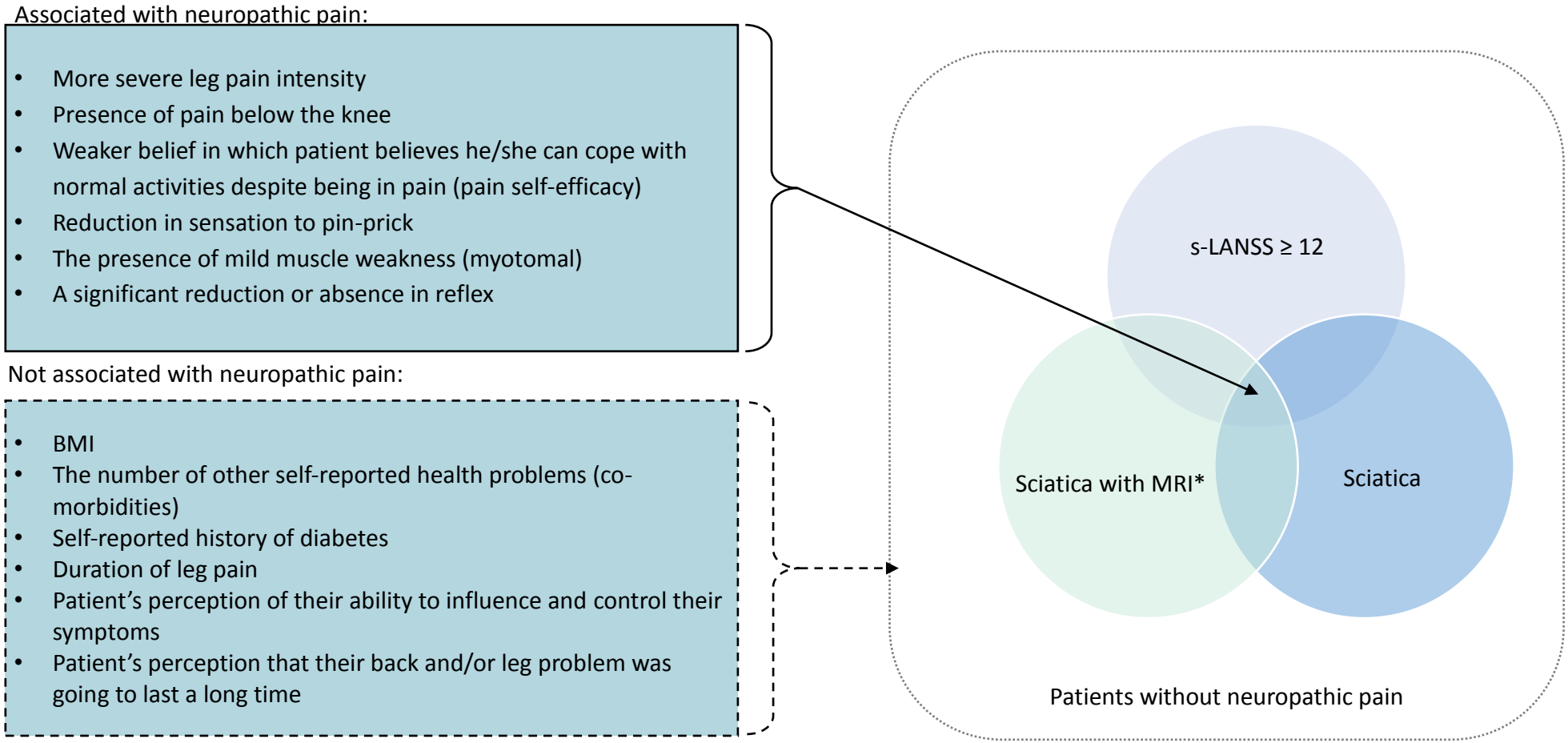
Abbreviations: MRI, magnetic resonance imaging. s-LANSS, self-report version of the Leeds Assessment of Neurological symptoms and signs

Figure 5.3 Characteristic associated with two definitions of neuropathic pain



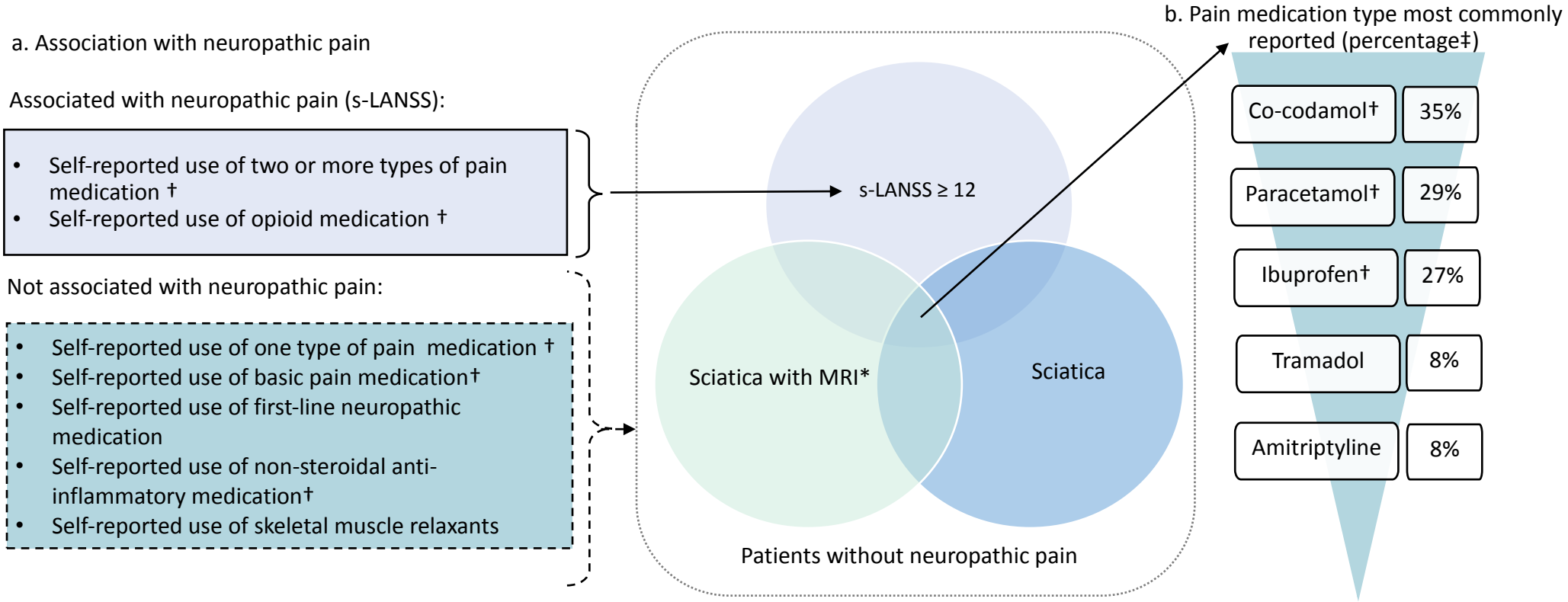
Abbreviations: MRI, magnetic resonance imaging. s-LANSS, self-report version of the Leeds Assessment of Neurological symptoms and signs
*Evidence of clear or possible nerve root compression on MRI

Figure 5.4 Characteristics consistently associated with neuropathic pain across all three definitions and characteristics that were similar between patients with and without neuropathic pain



Abbreviations: MRI, magnetic resonance imaging. s-LANSS, self-report version of the Leeds Assessment of Neurological symptoms and signs
*Evidence of clear or possible nerve root compression on MRI.

Figure 5.5 Summary of pain medication use in patients with and without neuropathic pain



Abbreviations: MRI, magnetic resonance imaging. s-LANSS, self-report version of the Leeds Assessment of Neurological symptoms and signs
*Evidence of clear or possible nerve root compression on MRI.
†Pain medications that include prescribed medications and those purchased over the counter
‡Percentages are given for one definition of neuropathic pain (s-LANSS ≥ 12) but were similar across all three definitions

5.6 Discussion

The aims of this research were to provide point prevalence estimates and to describe the characteristics of LBLP primary care patients with neuropathic pain, using case ascertainment tools and clinical examination to define cases of possible and/or probable neuropathic pain. As there is no "gold standard" diagnostic test for neuropathic pain, cases were defined in three ways, i) using s-LANSS, ii) clinical diagnosis of sciatica and iii) clinical diagnosis of sciatica with evidence of nerve root compression on MRI, to allow comparisons to be made. In this section, the baseline results are discussed and compared to previous literature. The strengths and weaknesses of these analyses are then discussed before considering some of the implications of the results for future research and clinical practice.

5.6.1 Prevalence

This is the first research, to the author's knowledge, that aimed to estimate the prevalence of neuropathic pain in LBLP patients consulting in primary care in the UK. The results of this research show there is considerable variation in the prevalence of neuropathic pain in this patient population depending on the definition used. The lower estimate was found in LBLP patients with probable neuropathic pain defined as having sciatica plus evidence of nerve root compression, the highest estimate was found in those patients with possible neuropathic pain defined as having a clinical diagnosis of sciatica (without taking into account MRI findings). Just under one quarter of patients were considered to have neuropathic pain consistently across all three definitions.

Similar to the prevalence estimates presented in this chapter, estimates derived from studies included in the systematic review in this thesis (the reader is referred to Chapter 3) varied considerably. In previous research using the s-LANSS to identify cases of neuropathic pain as in this research and in a similar patient population with LBLP, prevalence was estimated as 33% (based on research using 45 LBLP patients by Walsh and Hall (2009)) which is somewhat lower to the prevalence presented here (48%). Previous prevalence estimates of neuropathic pain based on clinical diagnosis of sciatica are barely more comparable. Based on one study of LBLP patients (n=51) with a clinical diagnosis of sciatica with evidence of nerve root compression based on MRI, prevalence was estimated to be 37% (Gierthmühlen et al. 2017). The variation in prevalence estimates derived from the current research and in comparison to those previously published highlights the complexity of defining neuropathic pain in this patient population.

Nearly a quarter of patients defined as having neuropathic pain using the most stringent definition (clinical diagnosis and evidence of nerve root compression on imaging), did not have neuropathic pain as defined by s-LANSS. Conversely, a proportion (11%) of patients in the study clinically diagnosed with referred leg pain had neuropathic pain as defined by s-LANSS. Sciatica is assumed to be neuropathic in nature (Dworkin 2002) but the evidence from this study and from others (for example the study by Mahn et al. (2011)), lends support to the argument that the pain mechanism underlying cases of sciatica is not exclusively neuropathic, or perhaps in some cases, non-neuropathic at all. On the other hand, referred pain which is assumed

to be due to nociceptive pain mechanisms (Bogduk 2009), may present with signs and symptoms of neuropathic pain, as suggested by the evidence from this and other studies (Walsh and Hall 2009, Schafer et al. 2011, Gierthmühlen et al. 2017). These results support the argument for the presence of distinct sub-groups of neuropathic pain in this patient population. In order to understand the potential relevance of sub-groups of LBLP patients with neuropathic pain it is important to understand the prognosis of this patient population. A starting point is to describe and understand the baseline characteristics of LBLP patients with neuropathic pain. The following section will discuss the baseline characteristics of LBLP patients with neuropathic pain in this research, and make comparisons with existing literature.

5.6.2 Baseline characteristics

5.6.2.1 Key findings

In this research, there was consistent evidence across the three definitions of neuropathic pain that leg pain intensity is higher compared to those without, pain is more commonly below the knee, and that LBLP patients with neuropathic pain report similar levels of back pain intensity compared to those without. Patients consistently (across three definitions) presented with mild (myotomal) muscle weakness and a significant reduction or loss of reflex and there was some but less consistent evidence of a presence of pins and needles, an increased pain response and neural tension. These characteristics provide an emerging description of the profile of this patient population. There was some consistent evidence (across two definitions) that patients report higher levels of LBLP-related disability which is comparable to other studies of

similar patient populations (Morsø et al. 2011, Schafer et al. 2011, Walsh and Hall 2009).

The findings on pain intensity are comparable to those of Morsø et al. (2011), which used PainDETECT to define neuropathic pain in LBLP patients. Other studies reported inconsistent findings on this variable, which is most likely due to presenting a composite score for pain including both low back and leg pain (Freynhagen et al. 2008, Schafer et al. 2011, Tutoglu et al. 2015, Walsh and Hall 2009, Gierthmühlen et al. 2017). That leg pain intensity is higher in this patient population may be important prognostic information as higher pain levels are associated with worse outcome in back pain patients in primary care (Dunn et al. 2011), and in patients with post-herpetic neuralgia (a condition which is considered neuropathic in nature) (Boogaard et al. 2015).

Similarly, the findings that LBLP patients with neuropathic pain consistently presented with pain below the knee is also comparable to the reports of several previous studies (Schafer et al. 2011, Smart et al. 2012a, Freynhagen et al. 2008, Beith et al. 2011). Pain below the knee was associated with neuropathic pain defined using PainDETECT (Beith et al. 2011) and as defined by clinical diagnosis (Schafer et al. 2011, Smart et al. 2012a, Freynhagen et al. 2008) in LBLP patients. In the current study, as in previously published literature, pain below the knee was common in patients with and without neuropathic pain, it is not clear whether having pain below the knee is a precise indicator of neuropathic pain.

5.6.2.2 Characteristics related to definition of neuropathic pain

Neuropathic pain is typically characterised by signs and symptoms that can be classified as either positive or negative (see Figure 1.1 (page 4) for a more detailed description of signs and symptoms of neuropathic pain). Patients with neuropathic pain defined using s-LANSS had more positive than negative signs and symptoms of neuropathic pain whereas those patients with neuropathic pain based on a clinical diagnosis of sciatica predominantly had negative signs. This provides evidence that the profile of patients with neuropathic pain defined using s-LANSS is distinct from those defined using clinical examination. This is not the first research to suggest that signs and symptoms vary between individual patients with neuropathic pain with the same clinical condition (for example see Mahn et al. (2011) and Baron et al. (2012)), and it is likely that the signs and symptoms of neuropathic pain represent variation in the underlying pathophysiological mechanisms in patients' presenting symptoms (Baron et al. 2017).

In the current research, characteristics related to sociodemographic profile, health status, LBLP-related pain severity and disability, psychological and illness perception variables, and history of either prescribed or over-the-counter pain medication in patients with and without neuropathic pain, were described for all three case definitions. There is evidence from previous research (see the results of a Systematic review in this thesis, Chapter 3, Section 3.4.3.2.3 (page 74) Psychological characteristics) that patients with neuropathic pain based on clinical examination present with fewer differences in characteristics such as depression and anxiety (for

example see Gierthmühlen et al. (2017), Walsh and Hall (2009) compared to those with neuropathic pain based on case ascertainment tools (for example, see Tutoglu et al. (2015), Uher and Bob (2013)). It is reasonable to suggest that the presence of more positive signs of neuropathic pain may be more distressing than negative signs and may explain why patients with neuropathic pain based on s-LANSS present with worse LBLP-morbidity, but based on the study design used in the research in this chapter this is purely speculative.

Previous research on neck and upper-limb pain patients with neuropathic pain based on clinical diagnosis, investigated similar characteristics in patients clinically diagnosed with neuropathic pain and reported that patients with “possible” and “probable” neuropathic pain were similar in terms of signs, symptoms, pain severity and pain medication use (Tampin et al. 2013). This is the first time to the author’s knowledge, that LBLP patients with “possible” and “probable” neuropathic pain based on clinical diagnosis have been compared. Imaging can be useful for identifying cases of serious pathology such as suspected cauda equina, suspected malignancy and following the traumatic onset of pain, and when invasive management options such as surgery are being considered. The argument raised by the findings of this research being that clinical diagnosis alone is sufficient for defining neuropathic pain, this is particularly the case for patients who consult in primary care where routine imaging is not recommended by clinical guidelines (NICE NG59 2016).

5.6.2.3 Psychological characteristics and pain duration

The presence of neuropathic pain was consistently associated with lower pain self-efficacy. Self-efficacy is a patient's degree of confidence in their ability to perform normal activities and tasks (such as household chores and increasing activity levels) despite being in pain. The current study provides new evidence that LBLP patients with neuropathic pain irrespective of definition, report lower pain self-efficacy. This research is the first to report pain self-efficacy in this specific population of LBLP patients with neuropathic pain, previous studies also found that patients with chronic pain thought to be neuropathic in nature reported less confidence in coping with pain compared to those with non-neuropathic pain. Previous research in LBP patients in primary care reported that pain self-efficacy was one of four psychological variables that was strongly related to worse back pain-related disability six months after consultation (Foster et al. 2010).

In this research there was no association between duration of leg pain and neuropathic pain and this was consistent across the three definitions of neuropathic pain. Longer back pain duration (greater than three months) was associated with neuropathic pain, defined by sciatica clinical diagnosis, but not in the other two definition of neuropathic pain. From previous studies that reported pain duration, there was some evidence that LBLP patients with neuropathic pain report similar pain duration to those patients without (Schafer et al. 2011, Gierthmühlen et al. 2017). In LBP populations, the duration of symptoms at baseline has been reported to influence the course (Hestbaek et al. 2003) and it is considered an important prognostic

indicator for poor outcome (Dunn et al. 2010). Although it is often assumed that neuropathic pain persists over time, it is not clear from the results of the current study and others, whether primary care LBLP patients with neuropathic pain go on to have persistent symptoms.

5.6.2.4 Pain medication use

In this research, LBLP patients with neuropathic pain commonly reported having been prescribed or purchased over-the-counter pain medication. Patients with neuropathic pain (across the three definitions) were no more likely to self-report having been prescribed or having purchased pain medication at baseline compared to those without. Patients with neuropathic pain based on s-LANSS presented with higher back pain intensity, worse health status and psychological morbidity and this in part may contribute to the increased use or prescription of medications found in this study. Few patients in this research reported having used specific medication for neuropathic pain and LBLP patients with neuropathic pain used specific medication for first line treatment of neuropathic pain no more often compared to those without. These results are comparable to previous studies reporting medication use in chronic pain patients with neuropathic pain (Torrance et al. 2007). In previous research, increased use of pain medication has been reported in LBLP patients with neuropathic pain based on clinical diagnosis (Freynhagen et al. 2008) and on PainDETECT (Morsø et al. 2011). It is not possible, using a cross-sectional study design, to investigate whether patients using pain medication gained effective pain relief and this is addressed further

using longitudinal data in Chapter 9, a detailed report of further limitations of this study design are provided in the section below.

5.6.3 Strengths and limitations

Strengths of this research include the large number of patients and the wide variety of characteristics, allowing a very detailed description of LBLP patients with and without neuropathic pain, in terms of their sociodemographic, pain and disability related characteristics as well as their general health and psychological profile. Additionally, this is the first research to describe prevalence and characteristics of LBLP patients with neuropathic pain by s-LANSS and also according to the NeupSIG definitions, first published by Treede et al. (2008) and updated by Finnerup et al. (2016). This is a novel approach for this patient population and in the absence of a gold standard for neuropathic pain, it provides interesting and useful insights.

Patients with neuropathic pain defined by a clinical diagnosis of sciatica and those with the more stringent neuropathic pain definition of sciatica and evidence of nerve root compression, shared large number of similarities in pain characteristics and findings of neurological examination. This is explained by the fact that these two definitions of neuropathic pain were defined in the same way (in terms of clinical assessment) other than the evidence of nerve root compression on MRI. Further to this, findings from neurological examination were found to be very strongly associated with neuropathic pain (defined as a clinical diagnosis of sciatica either with or without evidence of nerve root compression), the implication being a risk of bias. Incorporation bias can lead to an overestimation of the strength of an association between a characteristic and an

outcome, in this research neuropathic pain (Worster and Carpenter 2008). In this research, the comparison of patients with neuropathic pain defined in three ways, adds confidence about the characteristics of these patients, regardless of method of definition. Despite some evidence of incorporation bias in this research overall there is little impact on the main findings of the study.

Possible errors arising from the classification of pain medications (called misclassification bias) is a further limitation of the study design. An example of potential misclassification in research in this chapter is the categorisation of Co-codamol and Codeine. Co-codamol and Codeine in the current research were categorised as an opioid, however they are often purchased by patients over-the-counter in weak doses and it may be more representative to classify them as basic analgesia or as weak opioids. Research in Chapter 9 of this thesis addresses these problems using data collected from the review of medical records.

5.6.4 Implications for clinical practice and research

Clinicians working in primary care are often interested in questions concerning the presentation of conditions. Whilst cross-sectional research does not imply causality or any indication of timeline, it is useful for providing a description of a condition, in this instance, neuropathic pain in patients with LBLP. This research has identified that in many cases in primary care, LBLP may have underlying mechanisms that are neuropathic and LBLP patients with neuropathic pain consistently report higher leg pain intensity, pain below the knee and worse pain self-efficacy compared to those

without. They may also present with neurological changes on clinical examination characteristic of sensory loss.

This research reported large variation in prevalence estimates between definitions of neuropathic pain which highlights the complexity of identifying neuropathic pain in LBLP patients in the absence of a gold standard. Despite some consensus for the methods of defining neuropathic pain there is still considerable controversy (see Spahr et al. (2017) and Ochoa (2009) for examples) and there is an argument that the dichotomous nature of the classification system (patients either have pain that is nociceptive or neuropathic) is not appropriate for back pain patients (Kosek et al. 2016). Where conditions are difficult to define, or diagnose, prognosis of the condition becomes more important. There is a need for high quality research on the prognosis of LBLP patients with neuropathic pain, both in terms of determining clinical course (overall prognosis) and prognostic factors that are linked to the persistence of neuropathic pain over time.

LBLP patients with neuropathic pain based on PainDETECT have been reported to have higher mean pain intensity and higher mean pain-related disability over time compared to those patients without (Morsø et al. 2011). Analysis of longitudinal data in Chapter 6 will investigate the clinical course of LBLP patients with neuropathic pain at baseline based on the three definitions used in this chapter in terms of pain intensity and LBLP-related disability over time compared to those patients without. Characteristics including leg pain intensity, the presence of a reduction or loss to pin-prick sensation that may be associated with neuropathic pain at baseline will be used

in research found in later chapters (Chapter 8) investigating prognostic factors of persistent neuropathic pain in this patient population.

Finally, the current findings provide a snapshot of medication use in patients with and without neuropathic pain who had recently consulted their general practice. Research in Chapter 9 reports on a longitudinal analysis of electronic medical and prescribing records collected from GP surgeries of consenting patients in the ATLAS study which investigates the pain medications prescribed to patients with neuropathic pain at baseline.

5.7 Conclusions

In the research in this chapter, the prevalence and characteristics of LBLP patients with neuropathic pain were investigated. There was considerable variation in prevalence estimates between the three definitions of neuropathic pain (ranging from 46% to 74%). Patients with neuropathic pain (irrespective of neuropathic pain definition) reported higher leg pain intensity, worse pain self-efficacy, more frequently had pain below the knee compared to those without. Patients across all three definitions presented with negative signs of neuropathic pain, those with neuropathic pain based on s-LANSS presented with more positive signs than negative signs suggesting the profile of neuropathic pain varies within LBLP patients. Patients defined as having neuropathic pain based on the stringent definition of sciatica with evidence of nerve root compression on MRI presented with a similar profile as patients defined as having sciatica irrespective of imaging findings, suggesting that imaging in primary care is no more useful than clinical examination alone in the identification of cases of

neuropathic pain. Research in Chapter 6 will investigate the clinical course of LBLP patients with neuropathic pain using the three definitions described in this research, this will contribute to a better understanding of each of the three neuropathic pain profiles identified in the current chapter.

Chapter Six. Clinical course of patients with and without neuropathic pain consulting in primary care with low back-related leg pain

6.1 Introduction

Previous chapters of this thesis have highlighted the gaps in the published evidence from epidemiological research about the prognosis and the clinical course of LBLP patients with or without neuropathic pain (see Chapter 3 for results of a systematic review of the literature). This chapter describes the clinical course of LBLP patients with and without neuropathic pain in terms of pain intensity and LBLP-related disability, over three years. Comparisons are made between the results of this research and relevant literature, and the clinical and research implications of these findings are discussed.

6.2 Aims and objectives

6.2.1 Overall aim

To describe the clinical course of LBLP patients with neuropathic pain at baseline in terms of pain intensity and LBLP-related disability over short, intermediate and long term time points, and compare to those without.

6.2.2 Objectives

1. To provide a comparison of the clinical course of LBLP patients with and without neuropathic pain defined by case ascertainment tools and clinical examination in terms of pain intensity over a three year follow-up period.

2. To provide a comparison of the clinical course of LBLP patients with and without neuropathic pain defined by case ascertainment tools and clinical examination in terms of leg and back pain-related disability over a three year follow-up period.

6.3 Methods

Full details of the study design, data collection, methods used to identify cases of neuropathic pain have been described previously in this thesis (see Chapter 4, Study design and methods) and are summarised below in sections 6.3.1 to 6.3.3.

6.3.1 Study design

As in Chapter 5, the research presented in this chapter is based on secondary analysis of patients in the ATLAS cohort study. The reader is referred to Chapter 4, section 4.3 (page 112), for a detailed report of the population of interest, inclusion and exclusion criteria in the ATLAS study. The research in this chapter uses ATLAS cohort study data from baseline and then three follow-up points: four months, twelve months and three years.

6.3.2 Neuropathic pain definitions

Neuropathic pain in this chapter was based on the three definitions previously described in the research in Chapter 5. Two of the definitions of neuropathic pain could be described as “possible” neuropathic pain (those based on s-LANSS and a clinical diagnosis of sciatica), the third definition could be described as having

"probable" neuropathic pain (based on a clinical definition of sciatica with evidence of nerve root compression on MRI).

6.3.3 Measures of clinical course

Pain intensity and leg and back-related disability at baseline, four-months, twelve-months and three-years, were used to describe the clinical course of this patient population. Pain intensity was determined as the highest of mean leg pain intensity or mean back pain intensity in the previous two-weeks where leg pain was determined as the mean of three 0-10 NRS for current, usual and least leg pain over the previous two weeks and back pain as the mean of current, usual and least back pain over the previous two weeks. LBLP-related disability was measured using the RMDQ (Roland and Morris 1983) leg version (Patrick et al. 1995) which has 23 items scored from 0 to 23 with higher scores indicating higher disability.

6.4 Statistical analysis

Linear mixed-effect models were used to estimate the unadjusted mean of pain intensity and disability at all follow-up time-points (four months, twelve months and three years) in order to describe the clinical course of patients. The models included a neuropathic pain indicator variable by time interaction to obtain the estimated means (and 95% CI), at each follow-up time-point. Margins plots were used to summarise the information on the clinical course graphically. CI were obtained to evaluate the uncertainty of estimates with respect to missing data (Ibrahim et al. 2012). Models were fitted separately for pain intensity and disability. Further models were fitted to describe the effects of baseline scores on clinical course (adjusted mean and (95% CI))

by including the baseline pain intensity and separately baseline disability by time interaction in the model. This process was then repeated to investigate the clinical course of patients with and without neuropathic pain using the other definitions of neuropathic pain (based on a clinical diagnosis of sciatica with and without evidence of nerve root compression on imaging).

6.5 Results

6.5.1 Study population

Physiotherapy treatment received by patients with and without neuropathic pain based on the three definitions of neuropathic pain was largely similar (Table 6.1 summarises the treatment received by LBLP patients based on three definitions of neuropathic pain). The proportion of patients with neuropathic pain referred for further treatment or investigations ranged from 12.9% to 18.7% for three definitions of neuropathic pain. A higher proportion of patients with neuropathic pain based on a clinical diagnosis of sciatica with evidence of nerve root compression on MRI were referred for an epidural injection or for further investigation and management by spinal surgeons (14.3%, 36 out of 251) compared to those with neuropathic pain based on s-LANSS (7.5%, 22 out of 293) or sciatica without evidence of nerve root compression (8.0%, 36 out of 449). Few patients without a diagnosis of sciatica were referred for an epidural injection or to spinal surgeons (n=4). See Chapter 4, section 4.10 (page 138) for a report on the response to follow up and a description of baseline characteristics of patients who completed questionnaires at follow-up compared to those who did not.

Table 6.1 Treatment (care pathway) received by patients across three definitions of neuropathic pain

		Neuropathic pain definition					
		s-LANSS ≥ 12		*Clinical diagnosis of sciatica*		*Clinical diagnosis of sciatica with clear or possible evidence of nerve root compression*	
Care pathway (n=606)		*Yes, n=293*	*No, n=310*	*Yes, n=449*	*No, n=157*	*Yes, n=251*	*No, n=300*
Physiotherapy (0 to 2 sessions)		126 (43.0)	157 (50.7)	198 (44.1)	85 (54.1)	91 (36.3)	151 (50.3)
Physiotherapy (3 or more sessions)		126 (43.0)	125 (40.3)	193 (43.0)	60 (38.2)	113 (45.0)	127 (42.3)
Number of referrals for further treatment or investigation*		41 (14.0)	28 (9.0)	58 (12.9)	12 (7.6)	47 (18.7)	22 (7.3)
Referrals to/for	Pain specialists (pain clinic)	14 (4.8)	7 (2.3)	16 (3.6)	6 (3.8)	6 (2.4)	15 (5.0)
	Epidural injections or to spinal surgeons	22 (7.5)	18 (5.8)	36 (8.0)	4 (2.6)	36 (14.3)	4 (1.3)
	Spinal pain service (ESP practitioners)	9 (3.1)	10 (3.2)	15 (3.3)	5 (3.2)	12 (4.8)	7 (2.3)

Figures are frequencies (percentages)

S-LANSS, self-report version of Leeds Assessment for Neurological Symptoms and Signs neuropathic pain scale.

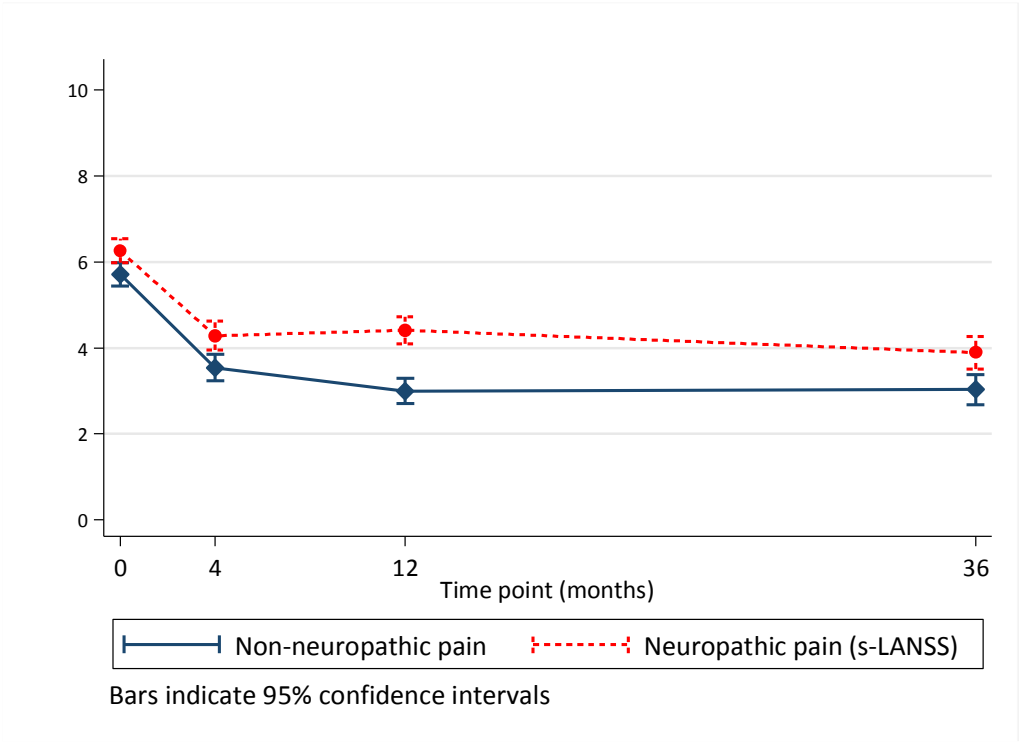
* Referrals were made for treatment (for example epidural injections, pain management) or for further investigation (including referrals to Extended Scope Physiotherapy (ESP) practitioners in a dedicated spinal pain service, spinal surgeons and pain specialists).

6.5.2 Clinical course of pain intensity

Pain intensity (the highest of either mean leg or mean back pain intensity) across all three definitions decreased over time and most of the change occurred between baseline and four-months (see Boxes 6.2 to 6.4 for a comparison of the pain intensity over three years in LBLP patients with neuropathic pain to those without). Mean (unadjusted) pain intensity of patients with neuropathic pain at baseline (across three definitions) ranged from 6.1 to 6.3, decreasing to between 3.8 and 4.3 at four-months. Improvement in pain intensity plateaued around four months and changed very little at three years for all three definitions (mean pain intensity of patients with neuropathic pain at three-years ranged from 3.3 to 3.9 for three definitions). When baseline pain intensity was adjusted for in all the three definitions, patients with neuropathic pain based on s-LANSS had significantly higher mean pain intensity at twelve months and three-years compared to those without, this difference was not consistent across the two other definitions. After adjusting for baseline scores, patients with neuropathic pain (based on a clinical diagnosis of sciatica) had lower mean pain intensity compared to those patients without; this was statistically significant at twelve months ($p = 0.011$) and at three years ($p=0.01$). Those patients with sciatica plus MRI evidence of nerve root compression had lower mean pain intensity at four months ($p=0.004$), twelve months ($p<0.001$) and at three years ($p=0.007$) compared to those without, after adjusting for baseline pain intensity.

Box 6.1 Three year clinical course (mean pain intensity) of patients with and without neuropathic pain (based on s-LANSS) at baseline*

Unadjusted clinical course



Bars indicate 95% confidence intervals

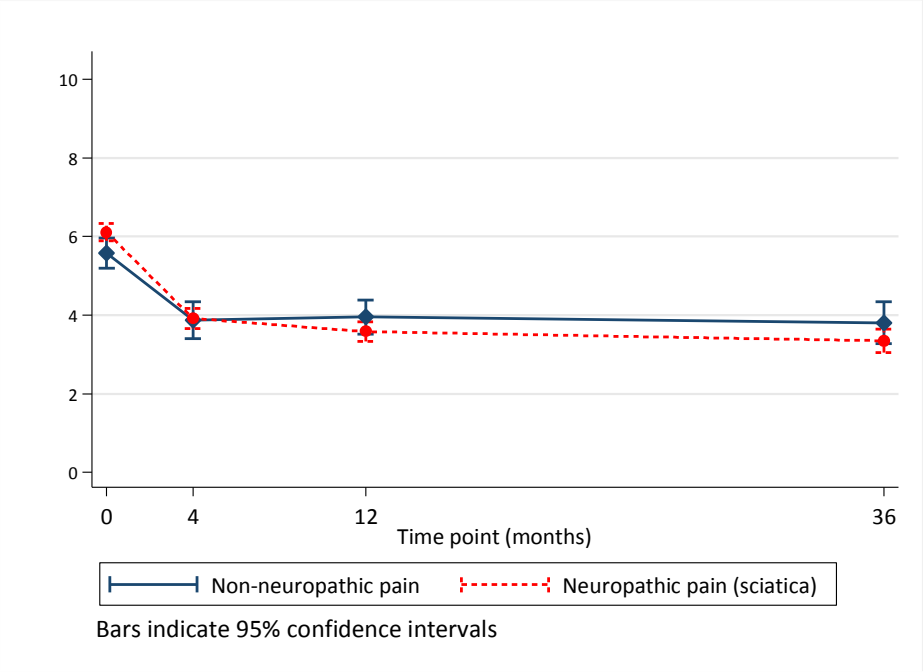
Clinical course adjusted for baseline pain score

Follow-up point	**Neuropathic pain (s-LANSS ≥ 12)**		**p**
	Yes, n=293 (48.4%)	No, n=313 (51.7%)	
Baseline	5.9 (5.7 to 6.1)	5.9 (5.7 to 6.1)	-
Four months	4.0 (3.8 to 4.3)	3.7 (3.4 to 4.0)	0.118
Twelve months	4.3 (4.0 to 4.5)	3.1 (2.8 to 3.3)	< 0.001
Three years	3.7 (3.4 to 4.1)	3.1 (2.8 to 3.4)	0.02

Abbreviations: NRS, numerical rating scale. s-LANSS, self-report version of the Leeds Assessment of Neuropathic Symptoms and Signs neuropathic pain scale. *Highest of leg or back pain intensity (mean of 3 NRS, 0-10)). 95% confidence intervals are shown in parentheses

Box 6.2 Three year clinical course (mean pain intensity) of patients with and without neuropathic pain (based on a clinical diagnosis of sciatica) at baseline*

Unadjusted clinical course



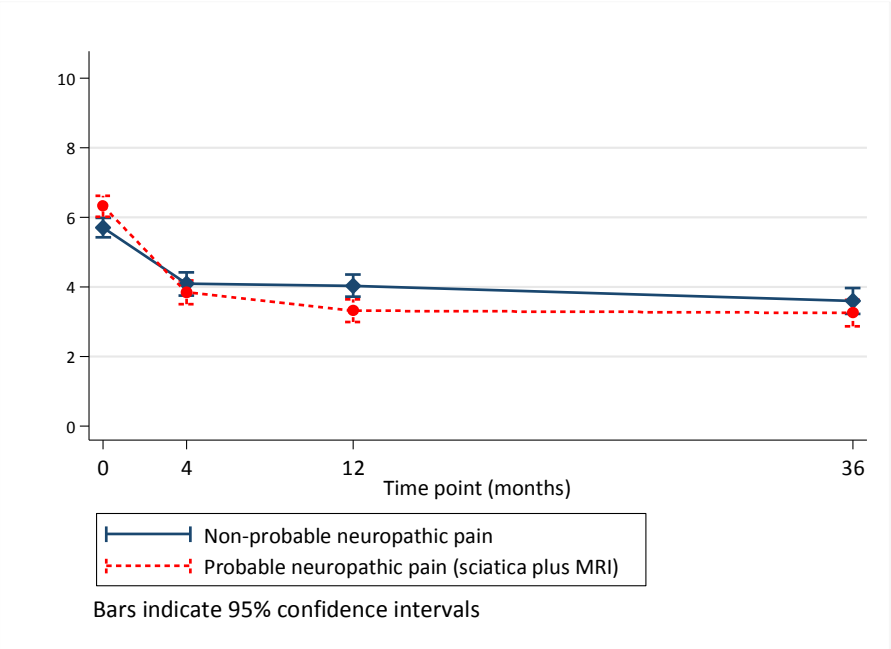
Clinical course adjusted for baseline pain score

Follow-up point	Neuropathic pain (clinical diagnosis of sciatica)		p
	Yes, n=452 (74.2%)	No, n=157 (25.8%)	
Baseline	5.9 (5.7 to 6.1)	5.9 (5.7 to 6.1)	-
Four months	3.8 (3.6 to 4.0)	4.1 (3.7 to 4.5)	0.205
Twelve months	3.5 (3.3 to 3.7)	4.1 (3.7 to 4.5)	0.011
Three years	3.2 (3.0 to 3.5)	4.0 (3.5 to 4.4)	0.01

Abbreviations: NRS, numerical rating scale.
*Highest of leg or back pain intensity (mean of 3 NRS, 0-10)). 95% confidence intervals are shown in parentheses

Box 6.3 Three year clinical course (mean pain intensity) of patients with and without neuropathic pain (based on a clinical diagnosis of sciatica with evidence of nerve root compression) at baseline*

Unadjusted clinical course



Bars indicate 95% confidence intervals

Clinical course adjusted for baseline pain score

Follow-up point	Neuropathic pain (clinical diagnosis of sciatica with evidence of nerve root compression)		p
	Yes, n=252 (45.5%)	No, n=302 (54.5%)	
Baseline	5.9 (5.7 to 6.1)	5.9 (5.7 to 6.1)	-
Four months	3.6 (3.3 to 3.9)	4.3 (4.0 to 4.5)	0.004
Twelve months	3.1 (2.8 to 3.4)	4.2 (3.9 to 4.4)	<0.001
Three years	3.0 (2.7 to 3.3)	3.7 (3.4 to 4.0)	0.007

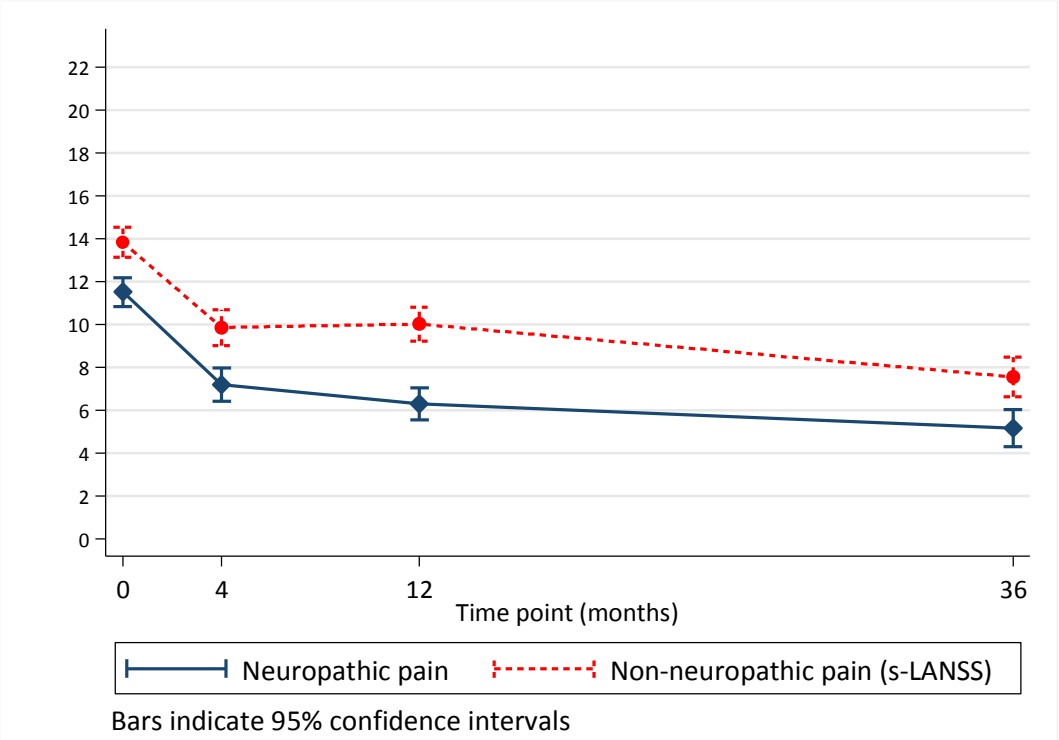
Abbreviations: NRS, numerical rating scale.
*Highest of leg or back pain intensity (mean of 3 NRS, 0-10)). 95% confidence intervals are shown in parentheses

6.5.3 Clinical course of leg and back pain-related disability

As with pain intensity, the course of LBLP patients with and without neuropathic pain, in terms of mean LBLP-related disability, improved over time for patients using all three definitions of neuropathic pain (see Boxes 6.4 to 6.6 for a comparison of LBLP-related disability over three years in patients with neuropathic pain to those without) and most of the change occurred between baseline (mean unadjusted RMDQ scores ranged from 12.9 to 13.8 across the three definitions) and four months (mean unadjusted RMDQ scores ranged from 8.6 to 11.5). Compared to patients without neuropathic pain, when baseline RMDQ scores were adjusted, patients with neuropathic pain based on s-LANSS had higher RMDQ scores at four months ($p=0.013$), at twelve months ($p<0.001$) and at three years ($p=0.016$). This finding was specific to patients with neuropathic pain based on s-LANSS; patients with neuropathic pain as defined by clinical diagnosis of sciatica (with or without evidence of nerve root compression) did not have significantly different RMDQ scores compared to those without. Patients without neuropathic pain defined using s-LANSS had lower LBLP related disability at follow-up compared to those patients without neuropathic pain defined by clinical diagnosis of sciatica either with or without evidence of nerve root compression.

Box 6.4 Three year clinical course (leg and back pain-related disability) of patients with and without neuropathic pain (based on s-LANSS) at baseline*

Unadjusted clinical course



Bars indicate 95% confidence intervals

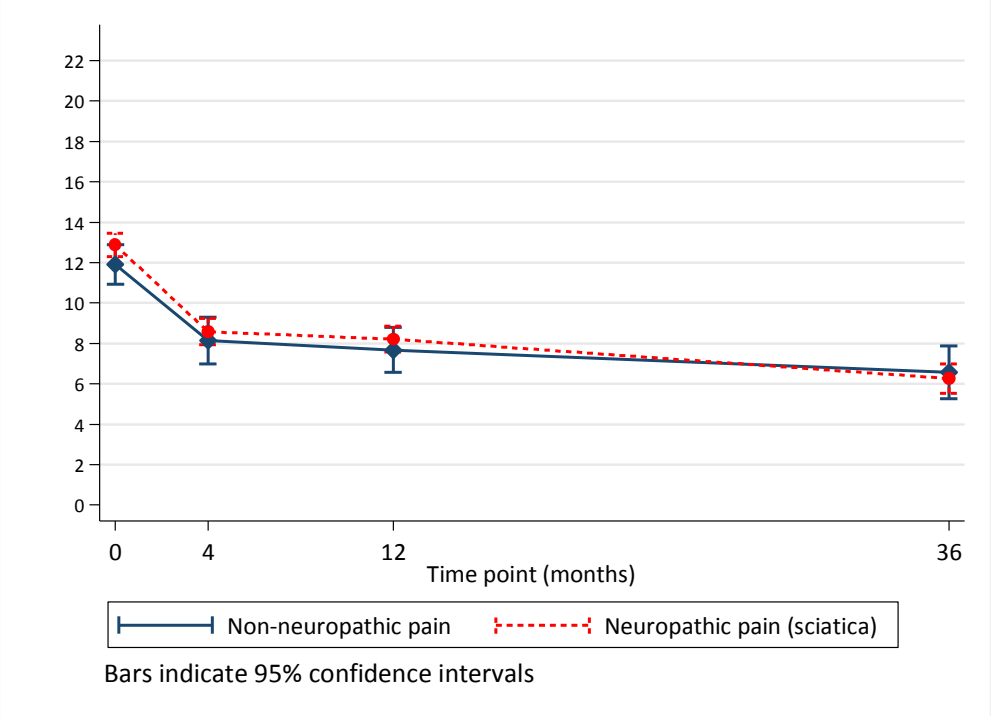
Clinical course adjusted for baseline RMDQ score

Follow-up point	**Neuropathic pain (s-LANSS ≥ 12)**		**p**
	Yes, n=293 (48.4%)	***No, n=313 (51.7%)***	
Baseline	12.3 (11.8 to 12.8)	12.3 (11.8 to 12.8)	-
Four months	9.0 (8.3 to 9.6)	7.7 (7.1 to 8.3)	0.013
Twelve months	9.2 (8.6 to 9.8)	6.7 (6.1 to 7.3)	<0.001
Three years	6.7 (6.0 to 7.4)	5.3 (4.7 to 6.0)	0.016

Abbreviations: NRS, numerical rating scale. RMDQ, Roland Morris Disability Questionnaire leg version. s-LANSS, self-report version of the Leeds Assessment of Neuropathic Symptoms and Signs neuropathic pain scale. *LBLP-related disability measured using RMDQ adapted for leg pain. 95% confidence intervals are shown in parentheses

Box 6.5 Three year clinical course (leg and back pain-related disability) of patients with and without neuropathic pain (clinical diagnosis of sciatica) at baseline*

Unadjusted clinical course



Bars indicate 95% confidence intervals

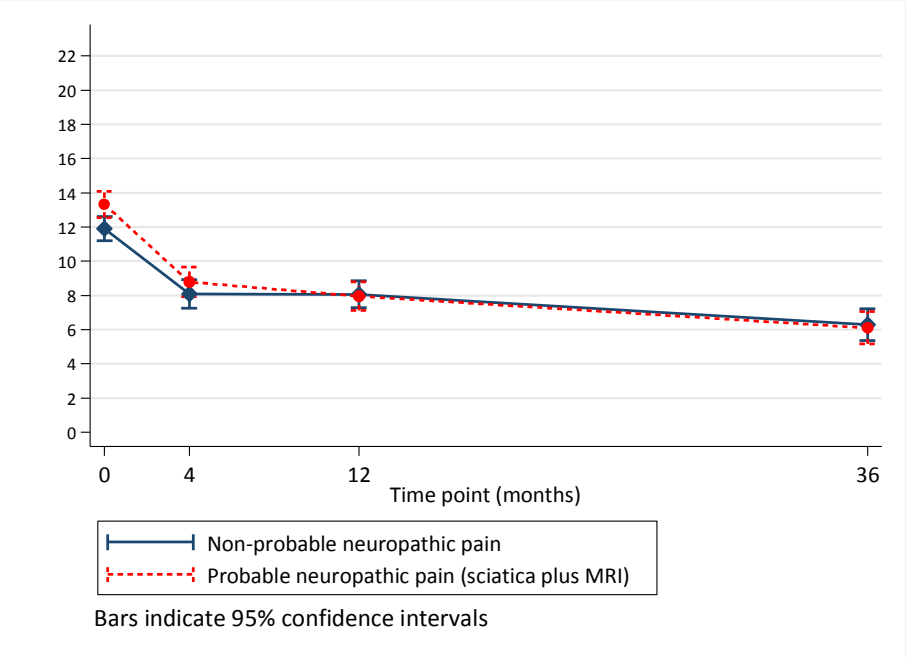
Clinical course adjusted for baseline RMDQ score

Follow-up point	Neuropathic pain (clinical diagnosis of sciatica)		p
	Yes, n=452 (74.2%)	No, n=157 (25.8%)	
Baseline	12.3 (11.8 to 12.8)	12.3 (11.8 to 12.8)	-
Four months	8.2 (7.7 to 8.7)	8.5 (7.6 to 9.4)	0.706
Twelve months	7.9 (7.4 to 8.3)	7.9 (7.1 to 8.8)	0.911
Three years	5.8 (5.2 to 6.3)	6.7 (5.7 to 7.7)	0.149

Abbreviations: NRS, numerical rating scale. RMDQ, Roland Morris Disability Questionnaire (RMDQ) leg version.
* LBLP-related disability measured using RMDQ adapted for leg pain. 95% confidence intervals are shown in parentheses

Box 6.6 Three year clinical course (leg and back pain-related disability) of patients with and without neuropathic pain (clinical diagnosis of sciatica with evidence of nerve root compression) at baseline*

Unadjusted clinical course



Clinical course adjusted for baseline RMDQ score

Follow-up point	**Neuropathic pain (clinical diagnosis of sciatica with evidence of nerve root compression)**		**p**
	Yes, n=252 (45.5%)	No, n=302 (54.5%)	
Baseline	12.2 (11.7 to 12.8)	12.2 (11.7 to 12.8)	-
Four months	8.1 (7.4 to 8.7)	8.4 (7.7 to 9.0)	0.554
Twelve months	7.3 (6.6 to 7.9)	8.3 (7.7 to 8.9)	0.047
Three years	5.4 (4.6 to 6.1)	6.2 (5.5 to 7.0)	0.15

Abbreviations: NRS, numerical rating scale. RMDQ, Roland Morris Disability Questionnaire (RMDQ) leg version.

* LBLP-related disability measured using RMDQ adapted for leg pain. 95% confidence intervals are shown in parentheses

6.6 Discussion

The research in this chapter investigates for the first time, the clinical course of LBLP patients consulting in primary care with and without neuropathic pain according to three definitions of neuropathic pain over short, intermediate and long-term follow-up. The clinical course of patients with and without neuropathic pain at baseline in terms of pain intensity and LBLP-related disability, showed some consistent similarities irrespective of the definitions used. Most improvement in both pain and disability occurred shortly after consultation in primary care, between baseline and four-months, followed by a plateau through to three years follow-up.

This pattern of improvement was expected as the clinical course of LBP patients has been shown to have a rapid pattern of improvement within the first three to four months, followed by further but smaller improvements, up to twelve months (Artus et al. 2014). The finding that the clinical course is worse in patients with neuropathic pain based on s-LANSS compares with previous research on the clinical course (over 12 months) of LBLP patients using PainDETECT to define neuropathic pain (Morsø et al. 2011). The course of patients with neuropathic pain based on clinical diagnosis of sciatica (with or without nerve root compression) was more favourable than that of patients with neuropathic pain based on s-LANSS. This supports the argument that the course of sciatica seems to be favourable in most cases (Vroomen et al. 2000) and suggests that the course of LBLP patients with neuropathic pain being worse than for those without, is dependent on the definition of neuropathic pain.

One of the assumptions underpinning the research in this thesis, and is supported by anecdotal and some empirical evidence is that the clinical course of patients with neuropathic pain is worse compared to those without. This would suggest that in the group of patients with "probable" neuropathic pain (those patients with a clinical diagnosis of sciatica with evidence of nerve root compression) the clinical course would be worse compared to those with "possible" neuropathic pain (those more broadly defined as a clinical diagnosis of sciatica without evidence of nerve root compression), but as reported above, this was not found. One potential reason for the course of this group of patients is that they may have received more targeted care, particularly by the twelve month follow-up; the majority of patients who were referred for an epidural injection or for further assessment and management by spinal surgeons, had a diagnosis of sciatica with evidence of nerve root compression on MRI. The suggestion being that variation in treatment received by study participants may have contributed to some imprecision in estimates in terms of pain intensity and LBLP-related disability; this being particularly so for patients with a clinical diagnosis of sciatica with or without evidence of nerve root compression. The absolute number of patients in this cohort who were referred for further treatment was low (between approximately one in five and one in eight depending on neuropathic pain definition). The differences in pain and disability between patients with and without neuropathic pain (with or without evidence of nerve root compression) were often small with no obvious clinical relevance. This adds some confidence that that the course of patients with sciatica (either with or without evidence of nerve root compression) was similar to those without.

This research provides evidence that challenges the perception that the clinical course of patients with neuropathic pain is worse compared to those without with the exception of those patients with neuropathic pain based on s-LANSS. It is clear from existing literature that the clinical course does not represent the course of individual LBP patients (Kongsted et al. 2016) but the average prognosis for a heterogeneous population, and there is growing epidemiological evidence from cohorts of LBP patients that distinct sub-groups of patients have different courses or trajectories (for example, Dunn et al. (2006)). This is also relevant to patients with neuropathic pain as it is thought that the underlying pathophysiological mechanisms are not homogenous across either LBP or LBLP (Baron et al. 2016). Research in future chapters will investigate the presence and clinical course of distinct sub-groups of patients with neuropathic pain.

6.6.1 Strengths and limitations

A strength of this study was the use of a large prospective cohort of patients to investigate the clinical course of patients with and without neuropathic pain based on more than one definition of neuropathic pain which allows for direct comparisons between definitions. A further strength is the use of mixed-effects models for repeated measures which take into account fixed effects (presence or absence of neuropathic pain at baseline), random effects (individual patients) and interaction between time and the outcome (pain intensity or LBLP-related disability) during model development.

Missing data was the main limitation of the research in this chapter. Fewer patients with neuropathic pain based on s-LANSS at baseline responded to follow-up, a slightly

higher proportion of patients had a diagnosis of sciatica and those who were followed up had lower RMDQ scores at baseline (see Chapter 4, section 4.10.2 (page 140) for a full report on response to follow-up). The implication of this being a risk of selection bias. Selection bias in cohort studies often relates to when there are differences in patients who are lost to follow-up compared to those who respond. In this research, missing data was accounted for by the use of mixed-effects models using likelihood-based approaches. Accounting for missing data in this way and separately adjusting for baseline pain intensity and disability provides some confidence in the key finding that the course of neuropathic pain rapidly improves and varies depending on definition.

6.6.2 Implications for clinical practice and research

This research contributes to an increased understanding of the nature of neuropathic pain which is important information for LBLP patients, clinicians and researchers. The key findings that: clinical course of neuropathic pain varies depending on the definition of neuropathic pain used, and the clinical course of patients with neuropathic pain is not always worse compared to those without, have implications for both clinical practice and future research. The information is important to researchers as there is ongoing debate about the best definition to use for neuropathic pain in both epidemiological and basic science research. Future research in this thesis will identify sub-groups of patients with neuropathic pain based on the change in presence of neuropathic pain over time.

6.7 Conclusions

In this chapter, the clinical course of LBLP patients with and without neuropathic pain, over a three year time period was investigated. LBLP patients with and without neuropathic pain at baseline improve in terms of pain intensity and LBLP-related disability, with the most improvement occurring between baseline and four months. The extent of the improvement in patients with neuropathic pain depended on the definition of neuropathic pain, only the clinical course of LBLP patients with neuropathic pain defined using s-LANSS seems to be worse compared to those without. Future chapters in this thesis will describe change in the presence of neuropathic pain over time and will describe the clinical course and prognostic factors of patients with persistent neuropathic pain.

Chapter Seven. Change in the presence of neuropathic pain in patients consulting in primary care with low back-related leg pain

7.1 Introduction

The previous chapter of this thesis highlighted that the clinical course of patients with neuropathic pain improves rapidly by short term follow up. This chapter describes LBLP patients with or without neuropathic pain at baseline in terms of the change in the presence or absence of neuropathic pain at baseline, short term, intermediate and long-term follow-up. The chapter first describes the frequency of neuropathic pain in LBLP patients at baseline and the three other time points. The chapter then identifies sub-groups of LBLP patients with or without neuropathic pain at baseline in terms of the change in the presence or absence of neuropathic pain over time before describing the baseline characteristics of these sub-groups. As in previous chapters, comparisons between the results of the research in this chapter and relevant literature are made and the clinical and research implications of these findings are then discussed.

7.2 Aims and objectives

7.2.1 Overall aim

To describe the change in the presence of neuropathic pain in LBLP patients with and without neuropathic pain at baseline over short, intermediate and long term time points.

7.2.2 Objectives

3. To describe the frequency of neuropathic pain over short, intermediate and long-term time points in LBLP patients who consult in primary care.
4. To identify distinct sub-groups of LBLP patients by the change in the presence of neuropathic pain over time.
5. To describe the baseline characteristics of sub-groups of LBLP patients identified by change in the presence of neuropathic pain.

7.3 Methods

Full details of the study design, data collection, methods used to identify cases of neuropathic pain, baseline characteristics and methods for handling missing data have been described previously in this thesis (see Chapter 4, Study design and methods) and are summarised below in sections 7.3.1 to 7.3.3.

7.3.1 Study design

As in previous chapters, the research presented in this chapter is based on secondary analysis of patients in the ATLAS cohort study. The reader is referred to Chapter 4, section 4.3 (page 112) for a detailed report of the inclusion and exclusion criteria in the ATLAS study. The research in this chapter uses ATLAS cohort study data from baseline and then three follow-up points, four months, twelve months and three years.

7.3.2 Neuropathic pain definitions

In the ATLAS dataset repeated measures of neuropathic pain were collected for one definition (based on s-LANSS) which could be described as “possible” neuropathic, this definition was used for the purpose of the research in chapter. S-LANSS data were collected at baseline and at all three follow-up time-points.

7.3.3 Baseline characteristics

The analyses in this chapter describe key baseline characteristics of LBLP patients that were selected based on the following: those characteristics that may be important to the prognosis of neuropathic pain in this patient population (consistent findings across at least two definitions of neuropathic pain presented in Chapter 5 (Prevalence and characteristics of neuropathic pain in primary care patients with LBLP)), those characteristics considered important to the prognosis of LBLP patients, alternative definitions of neuropathic pain and items from neurological examination. The baseline characteristics used in this chapter are briefly summarised below.

Table 7.1 Summary of key characteristics used to describe patients in research in Chapter seven

Baseline characteristics	Categorical scale	Continuous scale
Sociodemographic characteristics		
Female sex	Yes	-
Age	-	Years
Socio-economic status	Higher managerial, administrative and professional occupations	-
	Intermediate occupations	-
	Routine and manual occupations, never worked and long-term unemployed	-
Pain characteristics		
Leg pain intensity	-	0-10
Back pain intensity	-	0-10
Pain below the knee	Yes	-
Leg pain worse than back pain	Yes	-
Presence of pain in one leg	Yes	-
Duration of back pain symptoms in current episode	< 6 weeks	-
	6 to 12 weeks	-
	> 3 months	-
	< 6 weeks	-

Baseline characteristics	Categorical scale	Continuous scale
Duration of leg pain symptoms in current episode	6 to 12 weeks	-
	> 3 months	-
Widespread pain*	Yes	-
Limitations in activities		
RMDQ	-	0-23
Risk of persistent disabling pain (STarT Back)	Low risk	-
	Medium risk	-
	High risk	
Psychological variables		-
HADS (depression)	-	0-21
PSEQ†	-	0-60
Neurological examination findings		
Muscle strength† (Oxford scale 0-4)	5/5	-
	4/5	
	0/5 or 1/5 or 2/5 or 3/5	
Presence of either reduced or absent lower limb reflex	None	-
	Slightly reduced	-
	Significantly reduced or absent	-
Reduction or loss of sensation to pin-prick	Yes	-

Baseline characteristics	Categorical scale	Continuous scale
Presence of pins and needles	Yes	
Presence of allodynia or hyperalgesia in the leg(s) [§]	Yes	-
Neural tension test[||] (any positive test)	Yes	-
Other definitions of neuropathic pain		
Clinical diagnosis of sciatica[**]	Yes	-
Neuroimaging		
Evidence of nerve root compression on MRI	Yes	

Abbreviations: HADS, Hospital Anxiety and Depression scale. MRI, magnetic resonance imaging. PSEQ, pain self-efficacy questionnaire. RMDQ, Roland Morris Disability Questionnaire (RMDQ) leg version.
[*]Widespread pain was defined as pain present above and below the waist, in the right- and left-hand sides of the body and in the axial skeleton.
[†]†Higher scores on PSEQ reflect stronger self-efficacy beliefs
[‡]Muscle strength was tested according to a 6-point grading scale where;

0. No visible flicker of movement or contraction
1. Flicker of movement
2. Full active movement with gravity counterbalanced
3. Full active movement against gravity but not applied resistance
4. Full active movement against gravity and some applied resistance
5. Full active movement against gravity and strong resistance

[§] Hyperalgesia is and increased pain response to painful stimuli. Allodynia is pain response to non-painful stimuli (for example, brush strokes).
[||] Neural tension tests; straight leg raise, femoral stretch and slump test.
**Patients with a clinical diagnosis of sciatica are described as having “possible” neuropathic pain.

7.4 Statistical analysis

7.4.1 Frequency of neuropathic pain in LBLP patients over baseline, short, intermediate and long-term time points

The frequency (percentage) of neuropathic pain (based on s-LANSS definition) at each follow-up point over the three year time period along with 95% CI to describe the uncertainty around each point estimate, was estimated for LBLP patients at baseline and for those patients who responded to each subsequent follow-up point and had complete questionnaires for s-LANSS.

7.4.2 Change in the presence of neuropathic pain in LBLP patients

The different patterns of presenting with and without neuropathic pain per individual patient were tracked and the percentages of patients scoring 12 or greater or less than 12 were recorded at baseline and each time-point over three years. Sub-groups of patients were defined empirically a posteriori based on the change in the presence or absence of neuropathic pain over time. The proportion of patients in these sub-groups were reported with 95% CI. Descriptive statistics were used to report the characteristics of patients in each sub-group. This analysis was based on patients who completed the baseline assessment and who responded to questionnaires at follow-up (see Chapter 4 section 4.10.2 (page 139) for full details of differences between patients who did and did not respond to follow-up).

7.4.3 Missing data

The analyses presented in this chapter uses data from patients who completed questionnaires at baseline and at each follow-up point. To take into account the uncertainty due to missing data, analyses were also carried out combining the results from 60 multiply-imputed datasets (the reader is referred to Chapter 4, section 4.11 (page 148) for full details of the development of the imputation model and the assumptions made), a comparison of the two analyses was carried out which is summarised in section 7.5.4 and the results of these analyses are presented in the Appendix B.)

7.5 Results

7.5.1 Study population

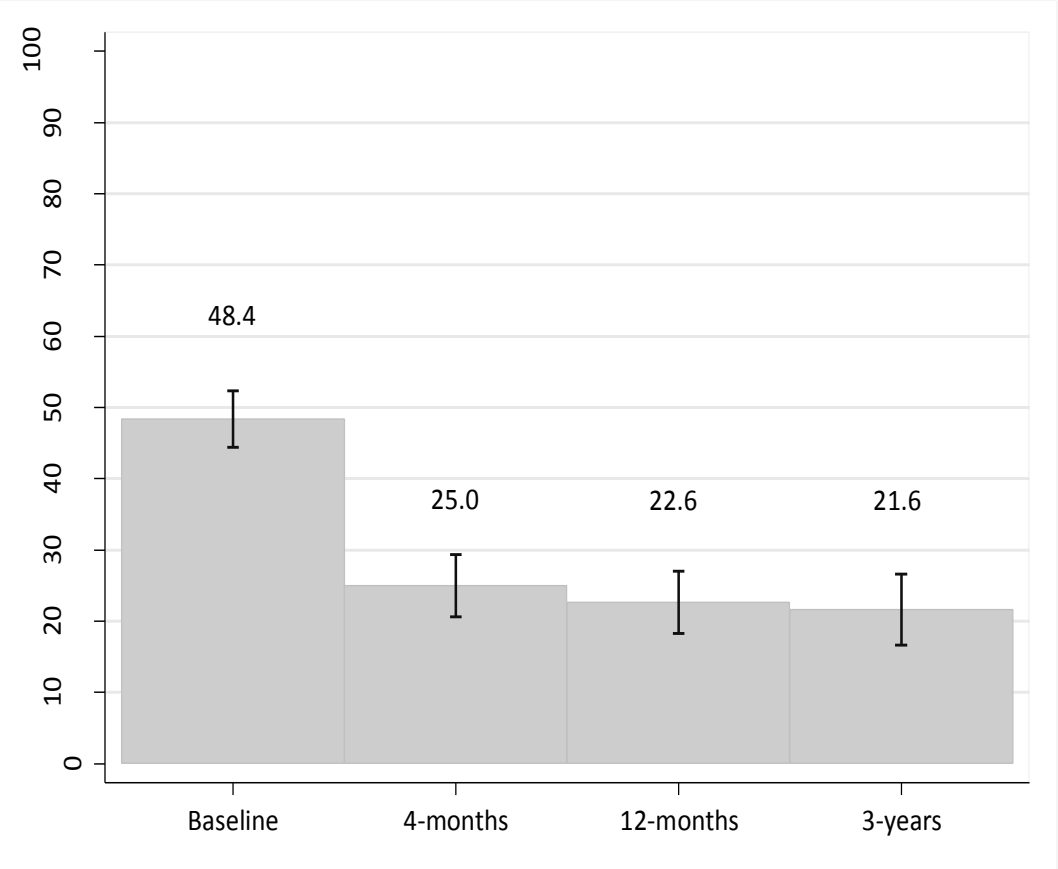
Of the 609 patients in the ATLAS study, 402 (66.0%) completed the study questionnaire at four-months, 450 (73.9%) at twelve months, and 316 (51.9%) at three-years. See Chapter 6, section 6.5.1 (page 217) for a full report on the treatments (care pathway) received.

7.5.2 Frequency of neuropathic pain at baseline, short, intermediate and long term time points

At baseline, nearly half of all LBLP patients had an s-LANSS score of 12 or greater. At four-months, a quarter of patients had a score of 12 or greater and this proportion remained similar at twelve-months and three-years. Figure 7.1 shows a summary of

the proportion of patients with neuropathic pain (based on s-LANSS) at baseline and at each of the three follow-up time-points.

Figure 7.1 Proportion of patients with neuropathic pain at baseline and at three subsequent follow-up time-points



Abbreviation: LBLP, low back-related leg pain. s-LANSS, self-report version of the Leeds Assessment of Neuropathic Symptoms and signs neuropathic pain scale.
Bars indicate 95% confidence intervals for certainty around the point estimate
*Shown as patients who responded to follow-up

7.5.3 Change in the presence of neuropathic pain in LBLP patients

Four sub-groups were identified by the change in the presence of neuropathic pain based on s-LANSS over a three-year follow-up period: those with non-neuropathic pain, those who demonstrated developing neuropathic pain, those with non-persistent

neuropathic pain, and those with long-standing persistent neuropathic pain. Patients with an s-LANSS score of less than 12 at baseline and each follow-up point thereafter and were included in the sub-group of non-neuropathic pain. Those with an s-LANSS score of less than 12 at baseline and 12 or greater at one or more follow-up points were included in the sub-group of developing neuropathic pain. Patients with an s-LANSS score of 12 or greater at baseline and at one (at most) of the three follow-up points were included in the sub-group of patients with non-persistent neuropathic pain. Patients with an s-LANSS score of 12 or greater at baseline and at two or more of the three follow-up points were described as having long-standing persistent neuropathic pain.

During the three-year study period, over four out of ten patients were described as having non-neuropathic pain, this was the largest sub-group of patients. The second largest (56 out of 199, 28.1%) was the sub-group described as having non-persistent neuropathic pain, the majority of change in the presence of neuropathic pain occurred by four months (33 out of 199, 16.6%). A small minority (12 out of 199, 6.0%) of patients had an s-LANSS score of 12 or greater at baseline and at all of the three follow-up points, these patients were included in the sub-group of patients with long-standing persistent neuropathic pain. A very small proportion of patients (3 out of 199, 1.5%) had an s-LANSS score of less than 12 at baseline and subsequently scored 12 or greater at all of the three follow-up points, this sub-group of patients were included in the sub-group of patients with developing neuropathic pain. Tables 7.2 and

7.3 summarise the change in the presence of neuropathic pain over time including the identification of sub-groups of patients with and without neuropathic pain.

Table 7.2 Change in the presence of neuropathic pain in patients over a three-year follow-up period.

Presence or absence of neuropathic pain over 3-years (s-LANSS)*				N (n=199)	Proportion (%)	95% Confidence Interval†	Sub-group
Baseline	**4 months**	**12 months**	**3 years**				
0	0	0	0	87	43.7	36.9 to 50.7	Non-neuropathic
0	0	0	1	6	3.0	1.4 to 6.6	Developing
0	0	1	0	7	3.5	1.7 to 7.2	Developing
0	0	1	1	1	0.5	0.0 to 3.5	Developing
0	1	0	0	3	1.5	0.0 to 4.8	Developing
0	1	0	1	2	1.0	0.0 to 4.0	Developing
0	1	1	0	2	1.0	0.0 to 4.0	Developing
0	1	1	1	3	1.5	0.0 to 4.8	Developing
1	0	0	0	33	16.6	12.0 to 22.5	Non-persistent
1	0	0	1	7	3.5	1.7 to 7.2	Non-persistent
				243			

Presence or absence of neuropathic pain over 3-years (s-LANSS)*				N (n=199)	Proportion (%)	95% Confidence Interval†	Sub-group
Baseline	4 months	12 months	3 years				
1	0	1	0	6	3.0	1.4 to 6.6	Non-persistent
1	0	1	1	5	2.5	0.1 to 5.9	Long-standing persistent
1	1	0	0	10	5.0	2.7 to 9.1	Non-persistent
1	1	0	1	5	2.5	0.1 to 5.9	Long-standing persistent
1	1	1	0	10	5.0	2.7 to 9.1	Long-standing persistent
1	1	1	1	12	6.0	3.4 to 10.4	Long-standing persistent

Abbreviation: s-LANSS, self-report version of the Leeds Assessment of Neuropathic Symptoms and signs neuropathic pain scale
*0 indicates s-LANSS score < 12 (non-neuropathic pain), 1 indicates s-LANSS score ≥ 12 (possible neuropathic pain)
†Confidence intervals are for certainty around a point estimate.

Table 7.3 Proportion of patients by neuropathic pain sub-group (n=199)

Sub-group*	N	Proportion (%)	95% Confidence Interval†
Non-neuropathic pain	87	43.7	36.9 to 50.7
Non-persistent neuropathic pain	56	28.1	22.3 to 34.8
Long-standing persistent neuropathic pain	32	16.1	11.6 to 21.9
Developing neuropathic pain	24	12.1	8.2 to 17.4

*Sub-groups: Non-neuropathic pain, s-LANSS < 12 at baseline and each follow-up point thereafter. Developing neuropathic pain, s-LANSS < 12 at baseline and ≥ 12 at one or more follow-up points. Non-persistent neuropathic pain, s-LANSS ≥ 12 at baseline and ≥ 12 at one (at most) of the three follow-up points. Longstanding persistent neuropathic pain, s-LANSS ≥ 12 at baseline and ≥ 12 at two or more of the three follow-up points.
†Confidence intervals are for certainty around a point estimate.

7.5.3.1 Baseline characteristics of patients by neuropathic pain sub-groups

Table 7.4 provides a summary of the baseline characteristics of patients by neuropathic pain sub-group. The subgroup with long-standing persistent neuropathic pain defined over the three year follow-up, reported the highest mean LBLP-related disability (13.6), this sub-group had the largest proportion of patients who were at high risk (STarT Back Tool score) of developing pain related persistent disability (50.0%), the lowest score for mean pain self-efficacy (31.4) and highest mean score for depression (7.5) (HADS). Patients in the sub-group of long-standing persistent neuropathic pain had the largest proportion of patients with allodynia and/or hyperalgesia (5 out of 32, 15.6%) and over nine out of ten (93.8%) patients had a clinical diagnosis of sciatica at baseline.

Patients with an s-LANSS score consistently less than 12 at baseline and all three follow-up points (the sub-group of non-neuropathic pain), reported the least severe LBLP-related morbidity. Patients in this sub-group had the lowest mean leg pain intensity (4.2), lowest mean LBLP-related disability (10.5), and highest mean pain self-efficacy (39.9). This sub-group also had the smallest proportion of patients with leg pain duration greater than three months (25.0%) and the smallest proportion of patients who were at high risk of pain-related persistent disability (20.0%). A substantial proportion of patients with non-neuropathic pain, according to s-LANSS, had a clinical diagnosis of sciatica (70.1%) with six out of ten patients (64.3%) having evidence of nerve root compression on imaging.

The sub-group with non-persistent neuropathic pain included the highest proportion of patients with muscle weakness (26.8%) at baseline, and more patients in this sub-group reported pain below the knee (82.1%). Patients in this sub-group reported high mean leg pain intensity (5.5), only the sub-group of patients with persistent neuropathic pain had higher scores for each of these characteristics. Patients in the sub-group of developing neuropathic pain, which was the smallest of the four sub-groups, reported the highest mean back pain intensity (5.6), the second highest mean score for HADS for depression (6.3), had the lowest proportion of patients with a clinical diagnosis of sciatica (66.7%) but the highest proportion with evidence of nerve root compression on MRI (81.0%).

Table 7.4 Baseline characteristics of patients by neuropathic pain sub-group over three-years (n=199)

		Neuropathic pain sub-group* over 3-years			
Baseline characteristic ***(All figures are frequencies (percentages) unless stated otherwise as mean (SD))***		*Non-neuropathic pain* *(n=87, 43.7%)*	*Non-persistent neuropathic pain* *(n=56, 28.1%)*	*Long-standing persistent neuropathic pain* *(n=32, 16.1%)*	*Developing neuropathic pain* *(n=24, 12.1%)*
Sociodemographic characteristics					
Female		49 (56.3)	38 (67.9)	19 (59.4)	15 (62.5)
Age, mean (SD)		54.3 (13.0)	54.4 (11.5)	55.1 (9.1)	57.3 (10.6)
Socio-economic status (n=194)	Higher managerial, administrative and professional occupations	23 (26.7)	14 (25.5)	5 (17.2)	12 (50.0)
	Intermediate occupations	26 (30.2)	14 (25.5)	5 (17.2)	6 (25.0)
	Routine and manual occupations, never	37 (43.0)	29 (52.7)	19 (65.5)	6 (25.0)

		Neuropathic pain sub-group* over 3-years			
Baseline characteristic ***(All figures are frequencies (percentages) unless stated otherwise as mean (SD))***		*Non-neuropathic pain* *(n=87, 43.7%)*	*Non-persistent neuropathic pain* *(n=56, 28.1%)*	*Long-standing persistent neuropathic pain* *(n=32, 16.1%)*	*Developing neuropathic pain* *(n=24, 12.1%)*
	worked and long-term unemployed				
Pain characteristics					
Leg pain intensity (0-10), mean (SD) (n=192)		4.2 (2.1)	5.5 (2.3)	5.7 (2.4)	5.4 (2.9)
Back pain intensity (0-10), mean (SD) (n=198)		4.7 (1.5)	5.0 (1.5)	5.2 (1.8)	5.6 (1.6)
Leg pain worse (n=198)		45 (51.7)	28 (50.9)	19 (59.4)	10 (41.7)
Pain location	Pain below the knee	58 (66.7)	46 (82.1)	27 (84.4)	16 (66.7)
	Pain in one leg	67 (77.0)	46 (82.1)	22 (68.8)	19 (79.2)
	Less than 6 weeks	33 (37.9)	21 (38.2)	12 (37.5)	12 (50.0)

Baseline characteristic ***(All figures are frequencies (percentages) unless stated otherwise as mean (SD))***		Neuropathic pain sub-group* over 3-years *Non-neuropathic pain* *(n=87, 43.7%)*	 *Non-persistent neuropathic pain* *(n=56, 28.1%)*	 *Long-standing persistent neuropathic pain* *(n=32, 16.1%)*	 *Developing neuropathic pain* *(n=24, 12.1%)*
Duration of back pain symptoms in current episode (n=198)	6 to 12 weeks	21 (24.1)	13 (23.6)	9 (28.1)	3 (12.5)
	> 3 months	33 (37.9)	21 (38.2)	11 (34.4)	9 (37.5)
Duration of leg pain symptoms in current episode greater > 3 months (n=193)	Less than 6 weeks	45 (52.9)	20 (37.0)	11 (36.7)	11 (45.8)
	6 to 12 weeks	18 (21.2)	16 (29.6)	5 (16.7)	3 (12.5)
	> 3 months	22 (25.9)	18 (33.3)	14 (46.7)	10 (41.7)
Widespread pain†		41 (48.2)	19 (34.6)	18 (56.3)	11 (45.8)
Limitations in activities and risk of persistent disabling pain					
LBLP-related disability (RMDQ, 0-23), mean (SD)		10.5 (5.5)	11.4 (5.2)	13.6 (5.7)	12.8 (5.4)

		Neuropathic pain sub-group* over 3-years			
Baseline characteristic ***(All figures are frequencies (percentages) unless stated otherwise as mean (SD))***		*Non-neuropathic pain* *(n=87, 43.7%)*	*Non-persistent neuropathic pain* *(n=56, 28.1%)*	*Long-standing persistent neuropathic pain* *(n=32, 16.1%)*	*Developing neuropathic pain* *(n=24, 12.1%)*
Risk of persistent disability due to back pain (STarT Back) (n=194)	Low risk	18 (21.2)	11 (20.4)	4 (12.5)	1 (4.4)
	Medium risk	50 (58.8)	25 (46.3)	12 (37.5)	14 (60.9)
	High risk	17 (20.0)	18 (33.3)	16 (50.0)	8 (34.8)
Psychological characteristics					
HADS (depression) (0-21), mean		5.2 (3.6)	5.1 (3.2)	7.5 (4.6)	6.3 (3.2)
PSEQ (0-60), mean (SD) ‡		39.9 (12.9)	37.2 (14.4)	31.4 (14.5)	36.6 (14.0)
Neurological examination findings					
Muscle strength§	5/5	70 (80.5)	41 (73.2)	28 (87.5)	21 (87.5)
	4/5	15 (17.2)	15 (26.8)	4 (12.5)	1 (4.2)

Baseline characteristic ***(All figures are frequencies (percentages) unless stated otherwise as mean (SD))***		Neuropathic pain sub-group* over 3-years			
		Non-neuropathic pain *(n=87, 43.7%)*	*Non-persistent neuropathic pain* *(n=56, 28.1%)*	*Long-standing persistent neuropathic pain* *(n=32, 16.1%)*	*Developing neuropathic pain* *(n=24, 12.1%)*
	0 to 3/5	2 (2.3)	0 (0.0)	0 (0.0)	2 (8.3)
Reflex change	None	75 (86.2)	45 (80.4)	21 (65.6)	21 (87.5)
	Slightly reduced	3 (3.5)	2 (3.6)	3 (9.4)	2 (8.3)
	Significantly reduced or absent	9 (10.3)	9 (16.1)	8 (25.0)	1 (4.2)
Reduction or loss of sensation to pin-prick		28 (32.2)	22 (39.3)	18 (56.3)	10 (41.7)
Presence of allodynia or hyperalgesia ||		2 (2.3)	5 (8.9)	5 (15.6)	2 (8.3)
Neural tension test (any positive test) **		41 (47.1)	32 (57.1)	21 (65.6)	13 (54.2)
Pins and needles		28 (32.2)	41 (73.2)	24 (75.0)	7 (29.2)
Other definitions of neuropathic pain					
Clinical diagnosis of sciatica††		61 (70.1)	47 (83.9)	30 (93.8)	16 (66.7)

	Neuropathic pain sub-group* over 3-years			
Baseline characteristic ***(All figures are frequencies (percentages) unless stated otherwise as mean (SD))***	*Non-neuropathic pain* *(n=87, 43.7%)*	*Non-persistent neuropathic pain* *(n=56, 28.1%)*	*Long-standing persistent neuropathic pain* *(n=32, 16.1%)*	*Developing neuropathic pain* *(n=24, 12.1%)*
Neuroimaging				
Evidence of nerve root compression on MRI (n=186)	54 (64.3)	27 (50.0)	18 (66.7)	17 (81.0)

Abbreviations: HADS, Hospital Anxiety and Depression scale. MRI, magnetic resonance imaging. PSEQ, Pain Self-Efficacy Questionnaire. RMDQ, Roland Morris Disability Questionnaire leg version. s-LANSS, self-report version of the Leeds Assessment of Neuropathic Symptoms and Signs neuropathic pain scale

*Sub-groups: Non-neuropathic pain, s-LANSS < 12 at baseline and each follow-up point thereafter. Developing neuropathic pain, s-LANSS < 12 at baseline and ≥ 12 at one or more follow-up points. Non-persistent neuropathic pain, s-LANSS ≥ 12 at baseline and ≥ 12 at one (at most) of the three follow-up points. Longstanding persistent neuropathic pain, s-LANSS ≥ 12 at baseline and ≥ 12 at two or more of the three follow-up points.

†Widespread pain was defined as pain present above and below the waist, in the right- and left-hand sides of the body and in the axial skeleton.

‡Higher scores on PSEQ reflect stronger self-efficacy belief

§ Muscle strength was tested according to a 6-point grading scale where;

0. No visible flicker of movement or contraction
1. Flicker of movement
2. Full active movement with gravity counterbalanced
3. Full active movement against gravity but not applied resistance
4. Full active movement against gravity and some applied resistance
5. Full active movement against gravity and strong resistance

|| Hyperalgesia is an increased pain response to painful stimuli. Allodynia is pain response to non-painful stimuli (for example, strokes)

** Neural tension tests; straight leg raise, crossover straight leg raise, femoral stretch and slump test

†† Patients with a clinical diagnosis of sciatica are described as having “possible” neuropathic pain

7.5.4 Comparison of complete case analysis versus imputed data

Estimates derived from complete case analysis and those based on imputed data were similar (the reader is referred to the Appendix B for the analysis in this chapter repeated using multiply imputes data). One exception where there were differences between estimates from complete case analysis and imputation was for evidence of nerve root compression, see Table 7.5 for a comparison between the two types of data.

Table 7.5 Evidence of nerve root compression across neuropathic pain sub-groups comparing imputed data and data using complete cases

	Estimates derived from complete case analysis		**Estimates derived from multiple imputation**	
Sub-group*	*N*	*Proportion (%)*	*Proportion (%)*	*95% Confidence Interval†*
Non-neuropathic pain	54	64.3	52.4	45.3 to 59.4
Non-persistent neuropathic pain	27	50.0	50.3	42.4 to 58.1
Longstanding persistent neuropathic pain	18	66.7	57.7	46.1 to 69.2
Developing neuropathic pain	17	81.0	60.3	47.4 to 73.3

*Sub-groups: Non-neuropathic pain, s-LANSS < 12 at baseline and each follow-up point thereafter. Developing neuropathic pain, s-LANSS < 12 at baseline and ≥ 12 at one or more follow-up points. Non-persistent neuropathic pain, s-LANSS ≥ 12 at baseline and ≥ 12 at one (at most) of the three follow-up points. Longstanding persistent neuropathic pain, s-LANSS ≥ 12 at baseline and ≥ 12 at two or more of the three follow-up points.

† Confidence intervals are for certainty around a point estimate for imputed data.

7.6 Discussion

The research in this chapter described the clinical course of LBLP patients by the change in the presence of neuropathic pain over time. This is the first research to the author's knowledge to investigate the change in the presence of neuropathic pain over time in this patient population using a prospective study design. In this cohort of LBLP patients consulting in primary care, the presence of neuropathic pain changes over time, resolving for most patients who have neuropathic pain at initial consultation and only remaining persistent in a few. A large proportion of patients had non-neuropathic pain over the short-term, intermediate and long-term follow up, and very few patients with non-neuropathic pain at baseline developed neuropathic pain at follow-up. Four sub-groups were identified based on the change in the presence of neuropathic pain over three years, those with non-neuropathic pain, developing neuropathic pain, non-persistent and longstanding persistent neuropathic pain. There were distinct differences in the patients' profiles of these four sub-groups and in particular the sub-group of patients with longstanding persistent neuropathic pain which was consistently found to have the most severe LBLP-related morbidity. This research challenges the common belief that neuropathic is persistent and is generally defined as a condition resulting from permanent nerve damage which is assumed to be irreversible (Merskey and Bogduk 1994).

Patients with non-neuropathic pain at each time-point, had the least pain intensity, least LBLP-related disability and least psychological symptoms at baseline, whereas patients with persistent neuropathic pain reported the most severe LBLP-related

morbidity. This was not unexpected and is consistent with the findings of research in Chapters 5 (Prevalence and characteristics of LBLP patients) and 6 (Clinical course of LBLP patients) that patients with non-neuropathic pain present with less severe pain-related morbidity and a more favourable course compared to those with neuropathic pain (based on s-LANSS).

In this research, sensory loss and central sensitisation were thought to be the underlying pain mechanisms associated with persistent and non-persistent neuropathic LBLP at baseline (see Chapter 5 for a full report of the profile of patients with neuropathic pain based on s-LANSS). From the findings from neurological examination there is evidence of sensory loss, which may be due to axonal damage in patients with and without persistent neuropathic pain, with sensory loss found in a higher proportion of those with non-persistent neuropathic pain. This may suggest the presence of mechanisms that resolve quickly in and around the nerve root in patients with non-persistent neuropathic pain. In contrast, patients in the sub-group with long-standing persistent neuropathic pain present at baseline with high levels of LBLP-related morbidity which may be explained in large part by central rather than peripheral pain mechanisms (Nijs et al. 2015, Smart et al. 2012b).

This research also identified a sub-group of patients with persistent neuropathic pain at four months, this sub-group was distinct in terms of presence of neuropathic pain because most of the change in the presence of neuropathic pain occurred by four months. This sub-group is interesting because the majority of improvement occurred between baseline and four months followed by a plateau thereafter which is

comparable to the time whereby the majority of tissue healing happens. This pattern of change between baseline and four months is similar to the pattern of rapid improvement in pain intensity and LBLP-related disability in patients with and without neuropathic pain reported in Chapter 6. It is likely that the course of patients with persistent neuropathic pain at four months is worse than those without, but this is not known. Identifying which patients will have persistent neuropathic at four months is important prognostic information for clinicians in primary care and may lead to better delivery of targeted treatments, such as neuropathic pain medication.

The proportion of patients in the sub-group of developing neuropathic pain who did not seem to have neuropathic pain at baseline but were characterised by the presence of neuropathic pain at a later point, has not previously been estimated. Previous research of primary care consulters reported the mean neuropathic pain score (using PainDETECT) increased over time in some patients with back pain alone (Hüllemann et al. 2017). The patient sub-group of developing neuropathic pain in this research had longer leg and back pain duration at baseline suggesting the underlying mechanisms may in part be time dependent. An example would be degenerative intervertebral discs which may initially give rise to nociceptive stimuli causing LBLP and over time involve microscopic nerve fibres giving rise to neuro-inflammation (Cohen and Mao 2014). In part, the underlying pain mechanisms in the sub-group of patients with developing neuropathic pain may well be explained by central sensitisation especially with the evidence that this sub-group present with highest back pain intensity and higher levels of depressive symptoms than patients in the non-neuropathic and non-

persistent neuropathic pain sub-groups. Previous research in patients with persistent post-surgical pain (which is thought to be a neuropathic pain condition) showed that patients with initial high pain intensity more often reported neuropathic signs and symptoms at follow-up (Phillips et al. 2014, Lavand'homme et al. 2014). The sub-group of patients with developing neuropathic pain was the smallest in the current research (n=24 or 12%), in 16 patients the presence of neuropathic pain was recorded at just one of the three follow-up points and it is not clear whether this represents real change in the presence of neuropathic pain, especially as it is known that case ascertainment tools such as s-LANSS may over-identify or may fail to identify some patients with neuropathic pain. For sub-groups to be clinically useful they should be stable over time (Kongsted et al. 2016) and this cannot be fully understood from this research, in part because of the small numbers. It would be of interest but out of the scope of this thesis, to investigate the epidemiology of patients with non-neuropathic pain who go on to develop neuropathic pain at a later point in time.

7.6.1 Strengths and limitations

The analyses in this research were based on a large prospective cohort of patients with long term follow-up, it is novel in its aims to investigate the change in presence of neuropathic pain over time in this patient population. A strength of this study was the use of techniques such as multiple imputation to account for missing data, observations derived from complete case analysis were similar to those based on imputed data. The exception being the observation that 81% patients in the sub-group of developing neuropathic pain were found to have evidence of nerve root

compression on MRI based on complete case analysis compared to 60% based on imputed data. The use of imputed data increased the confidence in interpreting the findings of this research.

A posteriori identification of sub-groups ensured that each sub-group was clinically meaningful and in the absence of any previous research this was a strength of this study. A limitation of this research is the use of one definition of neuropathic pain (s-LANSS) over time. It is possible that there may be important differences in the change in presence of neuropathic pain based on clinical examination over time compared to that based on s-LANSS. Similarly, the analysis in this research used data recorded at baseline and three follow-up time-points, this may contribute to uncertainty about the results for small sub-groups of patients with or without neuropathic pain, for example those with developing neuropathic pain. Data collection is a recognised challenge in epidemiology, particularly so in epidemiological research of neuropathic pain which is defined by many signs and symptoms collected by self-report and clinical examination.

7.6.2 Implications for clinical practice and research

Identification of the change of neuropathic pain over time improves the understanding of the prognosis of this condition in LBLP patients who consult in primary care. This research is important because it informs clinicians and, in turn, patients that neuropathic pain (based on s-LANSS) does change over time and it is not always persistent by nature. Some of the findings of this research should be interpreted in clinical practice with caution, in particular those describing the smallest sub-group of developing neuropathic pain.

Future research in this thesis will investigate the clinical course of patients with persistent neuropathic pain and will investigate whether potential prognostic factors collected from self-report and clinical examination can predict which patients will have persistent neuropathic pain at four months follow-up. Future research outside the scope of this thesis could usefully investigate whether there are any characteristics of patients without neuropathic pain at baseline that can successfully predict the presence of neuropathic pain at a later point in time.

7.7 Conclusions

In this chapter, change in the presence of neuropathic pain over a three year time period was investigated. Neuropathic pain is not always persistent by nature, but it does remains persistent in a few patients over three years (16%) and these patients have the most severe LBLP-related disability. Change in presence of neuropathic pain in LBLP patients with neuropathic pain (based on s-LANSS) at baseline most commonly occurs by four months. Future chapters will investigate whether the clinical course of this sub-group of patients with persistent neuropathic pain at four months is worse compared to those without and will identify prognostic factors that are associated with persistent neuropathic pain at four months.

Chapter Eight. Prognosis of LBLP patients with neuropathic pain: Characteristics, clinical course and prognostic factors

8.1 Introduction

The systematic review in Chapter 3 highlighted a paucity of prognosis research and an absence of prognostic factor research in this patient population with neuropathic pain. Prognostic factors are characteristics of persons with a condition that are associated with a subsequent health outcome, in the context of this research characteristics of LBLP patients with neuropathic pain associated with persistent neuropathic pain. In this thesis, potential prognostic factors in LBLP patients with neuropathic pain were identified in part during cross-sectional analysis of data from LBLP patients with and without neuropathic pain, based on three definitions of neuropathic pain at baseline (see Chapter 5). In patients with neuropathic pain at baseline, most of the change in the presence of neuropathic pain occurred by four months which corresponds to the time that normal tissue healing takes place (Chapter 7). LBLP patients with persistent neuropathic pain were identified in the previous chapter and are of interest because this sub-group of patients were characterised as having worse pain intensity and disability at baseline compared to those in the non-neuropathic pain sub-group and those with non-persistent neuropathic pain. This chapter reports on the characteristics, clinical course and prognostic factors of LBLP patients with neuropathic pain that may be associated with the outcome of persistent neuropathic pain. The results of this research are reported and comparisons made to relevant literature, before a discussion of the clinical and research implications of these results.

8.2 Aims and objectives

8.2.1 Overall aim

To investigate the overall prognosis of LBLP patients with neuropathic pain, in terms of clinical course and exploratory prognostic factor research.

8.2.2 Objectives

1. To describe the baseline characteristics of patients with and without persistent neuropathic pain at four months.

2. To compare the clinical course in terms of pain intensity, leg and back pain-related disability over a three year follow-up period of patients with and without persistent neuropathic pain at four months.

3. To identify potential prognostic factors associated with the outcome of persistent neuropathic pain in patients with neuropathic pain at baseline.

4. To investigate the prognostic value of potential prognostic factors of LBLP patients with neuropathic pain that may be associated with persistent neuropathic pain.

8.3 Methods

Full details of the study design, data collection, methods used to identify cases of neuropathic pain and methods for handling missing data have been described in previous chapters (Chapter 4). Sections 8.3.1 to 8.3.4 summarise the details which are relevant to the research in this chapter.

8.3.1 Study design

The research in this chapter is based on secondary analysis of the ATLAS study cohort using those LBLP patients with neuropathic pain at baseline.

8.3.2 Data collection

Data were collected at baseline and then the follow-up points at four months, twelve months and three years.

8.3.3 Neuropathic pain definitions

The analyses reported in this chapter were based on two definitions describing persistent neuropathic pain: (i) an s-LANSS score of 12 or above at baseline and at four months (Chapter 7 provided details of how the sub-group of patients with persistent neuropathic pain based on s-LANSS were identified); and (ii) a clinical diagnosis of sciatica at baseline and the presence of pain below the knee at four months, where pain below the knee was used as a proxy for sciatica (Dionne et al. 2008). In the absence of clinical examination, there is some evidence that the presence of pain below the knee can be a useful proxy indicator for a diagnosis of sciatica (Konstantinou et al. 2012c). The reader is referred to Chapter 4, section 4.5 (page 116) for details of how patients in this research were diagnosed with sciatica.

8.3.4 Measures

8.3.4.1 Baseline characteristics

Key baseline characteristics of LBLP patients with persistent neuropathic pain compared to those without are described. The method of data collection for key characteristics is briefly summarised below in Table 8.1. The reader is referred to Chapter 4, section 4.9 (page 120) for a full description of the method of data collection for each characteristic.

Table 8.1 Summary of key characteristics used to describe patients with persistent neuropathic pain in research in Chapter eight

Baseline characteristics	**Categorical scale**	**Continuous scale**
Sociodemographic characteristics		
Female sex	Yes/no	-
Age	-	Years
Socio-economic status	Higher managerial, administrative and professional occupations	-
	Intermediate occupations	-
	Routine, manual occupations, never worked and long-term unemployed	-
Pain characteristics		
Leg pain intensity	-	0-10

Baseline characteristics	Categorical scale	Continuous scale
Back pain intensity	-	0-10
Pain below the knee	Yes/no	-
Leg pain worse than back pain	Yes/no	-
Duration of back pain symptoms in current episode	< 6 weeks	-
	6 to 12 weeks	-
	> 3 months	-
Duration of leg pain symptoms in current episode	< 6 weeks	-
	6 to 12 weeks	-
	> 3 months	-
Limitations in activities		
LBLP-related disability (RMDQ)	-	0-23
Psychological variables		
HADS (depression)	-	0-21
Pain self-efficacy (PSEQ)*	-	0-60
Neurological examination findings		
Presence of muscle weakness†	5/5	-
	4/5	-
	0 to 3/5	-
Presence of either reduced or absent lower limb reflex	None	-
	Slightly reduced	-

Baseline characteristics	Categorical scale	Continuous scale
	Significantly reduced or absent	-
Reduction or loss of sensation to pin-prick	Yes/no	-
Presence of pins and needles	Yes/no	-
Presence of allodynia or hyperalgesia in the leg(s) [‡]	Yes/no	-
Neural tension test[§] (any positive test)	Yes/no	-
Neuroimaging		
Evidence of nerve root compression on MRI	Yes/no	-

Abbreviations: HADS, Hospital Anxiety and Depression scale. MRI, magnetic resonance imaging. PSEQ, pain self-efficacy questionnaire. RMDQ, Roland Morris Disability Questionnaire leg version.

[*] Higher scores on PSEQ reflect stronger self-efficacy beliefs

[†] Muscle strength was tested according to a 6-point grading scale where;

6. No visible flicker of movement or contraction
7. Flicker of movement
8. Full active movement with gravity counterbalanced
9. Full active movement against gravity but not applied resistance
10. Full active movement against gravity and some applied resistance
11. Full active movement against gravity and strong resistance

[‡] Hyperalgesia is and increased pain response to painful stimuli. Allodynia is pain response to non-painful stimuli (for example, brush strokes).

[§] Neural tension tests; straight leg raise, femoral stretch and slump test.

8.3.4.2 Clinical course

As in chapter 6, the analyses in this chapter compare the clinical course of patients in terms of pain intensity and leg and back-pain related disability at four, twelve months and three years. Pain intensity was determined as the highest mean of three 0 to 10 NRSs for current, usual and least leg or back pain intensity in the previous two weeks.

LBLP-related disability was measured using the leg version of RMDQ (0 to 23) with higher scores indicating more severe disability.

8.4 Statistical analysis

8.4.1 Baseline characteristics

Descriptive analysis (mean and SD for continuous variables and frequency and percentage for categorical variables) was used to report the characteristics of the LBLP patients with and without persistent neuropathic pain. This analysis was based on patients who completed both the baseline and the follow-up questionnaires at four months.

8.4.2 Clinical course

The clinical course of patients with and without persistent neuropathic pain was examined over the three year study period using repeated-measure linear mixed-effect models to compare the unadjusted means of pain intensity and separately LBLP-related disability at baseline and all three follow-up points. The reader is referred back to Chapter 6, Section 6.4.3 Statistical analysis for a detailed report on how models were developed. Further models were developed adjusted for baseline pain intensity and then disability.

8.4.3 Exploratory prognostic factor research

8.4.3.1 Start and end points

To identify prognostic factors in LBLP with neuropathic pain, two different start and end points were identified depending on the definition of persistent neuropathic pain.

Firstly, for the definition of persistent neuropathic pain based on s-LANSS, the start point was s-LANSS score of 12 or greater at baseline and the end-point was persistent neuropathic pain based on s-LANSS at four months. Patients with s-LANSS score of 12 or above at baseline and score less than 12 at four months were defined as having non-persistent neuropathic pain. Secondly, for the definition of persistent neuropathic pain based on a clinical diagnosis of sciatica the start point was clinical diagnosis of sciatica at baseline and the end point was the presence of pain below the knee at four months. Patients with a clinical diagnosis of sciatica at baseline and pain below the knee at four months were defined as having persistent neuropathic pain, and those with a clinical diagnosis of sciatica at baseline with an absence of pain below the knee at four months were defined as having non-persistent neuropathic pain.

8.4.3.2 Identification of potential prognostic factors

The decision to include certain characteristics as potential prognostic factors was made on the condition of each characteristic fulfilling one or more of five criteria. Box 8.1 provides details of each of these five items.

Box 8.1 Criteria for investigating prognostic factors

Factors were chosen on the condition of:

A. Consistent associations with neuropathic pain across three definitions in LBLP patients*, or
B. Known to be associated with poor outcomes in broader LBP populations, or
C. Known to be important to underlying pathophysiological mechanisms of neuropathic pain, or
D. Considered to be definitions of neuropathic pain, and
E. Availability in the dataset

*(see Chapter 5, Section 5.5.5 (page 196) for a summary of the consistent findings across three definitions of neuropathic pain)

In addition to these five criteria, consideration was given to whether potential prognostic factors were closely related. Where prognostic factors were thought to be closely related, correlation coefficients were estimated and if correlation was present ($r > 0.7$) one of the two potential prognostic factors was dropped to limit the effects of collinearity. Priority was given to the prognostic factor with more consistent associations with neuropathic pain across three definitions. Characteristics were selected as potential prognostic factors, Table 8.2 lists these and summarises the criteria under which they were chosen. In preparation for analysis, selected prognostic factors that were continuous in the dataset were retained as continuous variables, all other factors were categorical and dummy variables were created for prognostic factors with more than two categories. The reader is referred back to Chapter 4 (section 4.8 (page 119) and section 4.9 (page 120)) for details of how each of the factors were categorised.

Table 8.2 Selected potential prognostic factors

Prognostic factor	Criteria*	Type of variable
Age	B	Continuous
Female sex	B	Binary
Socioeconomic status	B, E	Categorical
Leg pain duration in the current episode	B, E	Categorical
Leg pain intensity	A, B, E	Continuous
Pain self-efficacy	A, E	Continuous
Clinical diagnosis of sciatica†	D, E	Binary
s-LANSS score of 12 or greater†	D, E	Binary
Clear or possible nerve root compression on MRI	C, E	Binary
Reduction or loss in sensation to pin-prick	A, C, E	Binary
Presence of pins and needles	C, E	Binary
Pain below the knee	A, C, E	Binary

*Factors were chosen on the condition of:

Criteria

A. Consistent associations with neuropathic pain across three definitions in LBLP patients
B. Known to be associated with poor outcomes in broader LBP populations
C. Known to be important to underlying pathophysiological mechanisms of neuropathic pain
D. Considered to be definitions of neuropathic pain
E. Availability in the dataset

† Either/ or potential factor was used depending on start and end-point

8.4.3.3 Identification and prognostic value of factors associated with persistent neuropathic pain

Binary logistic regression was used to examine the associations between any potential prognostic factor and the end-point, persistent neuropathic pain (based on two definitions). Factors were considered for multivariable logistic regression based on the strength of association with either definition of persistent neuropathic pain ($p<0.25$). Other factors considered for the multivariable model were those with greater clinical relevance (age, female sex, leg pain intensity and leg pain duration). It has been suggested that the number of events of the outcome per potential prognostic factor should not be less than one factor per ten events (Peduzzi et al. 1996). Given the size of the smallest sample in the analyses was 164 with 44% (n=72) having persistent neuropathic pain, a multivariable model had sufficient power to assess seven prognostic factors. Age, female sex, leg pain intensity and leg pain duration accounted for five factors giving sufficient power to investigate the prognostic value for a maximum of two further potential prognostic factors. Odds ratios with 95% confidence intervals and p values were reported to determine the strength of association of the chosen prognostic factors. This analysis combines results from 60 multiply-imputed datasets to take into account the uncertainty due to missing data. Please refer to Chapter 4, section 4.11.1 (page 148) for full details of the development of the imputation model and the assumptions made.

8.5 Results

8.5.1 Baseline characteristics

8.5.1.1 Persistent neuropathic pain based on s-LANSS

In total, 44% (72 out of 164) of patients with neuropathic pain (based on s-LANSS) had persistent neuropathic pain at four months. Table 8.3 summarises the baseline characteristics of LBLP patients with persistent neuropathic pain compared to those with non-persistent neuropathic pain. They had similar mean back pain intensity, but higher leg pain intensity (6.2 (2.3) vs 5.6 (2.2)), higher mean LBLP-related disability scores (using RMDQ 0 to 23, (14.9 (5.1) vs 12.4 (5.4)) and higher depressive symptoms (using HADS 0 to 21, 7.9 (4.3) vs 5.9 (3.5), where scores 7 or below are indicative of non-clinical levels of symptoms). Higher proportions of patients with persistent neuropathic pain had evidence of nerve root compression on MRI (60.9%, 39 out of 64) compared to those without (50.6% (43 out of 85).

Table 8.3 Baseline characteristics of patients with and without persistent neuropathic pain (based on s-LANSS)

Baseline characteristics (n=164)*	**†Persistent neuropathic pain (s-LANSS ≥12 at baseline and at four months)**	
	Yes (n=72, 44%)	*No (n=92, 56%)*
Sociodemographic characteristics		
Female	45 (62.5)	62 (67.4)
Age, mean (SD)	53.7 (13.0)	53.3 (12.3)

Baseline characteristics (n=164)*		**†Persistent neuropathic pain (s-LANSS ≥12 at baseline and at four months)**	
		Yes (n=72, 44%)	*No (n=92, 56%)*
Socio-economic status (n=157)	Higher managerial, administrative and professional occupations	15 (16.7)	9 (13.4)
	Intermediate occupations	24 (26.7)	17 (25.4)
	Routine and manual occupations, never worked and long-term unemployed	51 (56.7)	41 (61.2)
Pain characteristics			
Leg pain intensity (0-10), mean (SD) (n=157)		6.2 (2.3)	5.6 (2.2)
Back pain intensity (0-10), mean (SD) (n=162)		5.6 (1.7)	5.2 (5.6)
Pain below the knee		60 (83.3)	72 (78.3)
Leg pain worse than back pain (n=163)		37 (51.4)	50 (55.0)
Duration of back pain symptoms in current episode (n=163)	< 6 weeks	35 (38.5)	24 (33.3)
	6 to 12 weeks	22 (24.2)	13 (18.1)
	> 3 months	34 (37.4)	35 (48.6)
	< 6 weeks	35 (39.3)	23 (33.8)

Baseline characteristics (n=164)*		**†Persistent neuropathic pain (s-LANSS ≥12 at baseline and at four months)**	
		Yes (n=72, 44%)	*No (n=92, 56%)*
Duration of leg pain symptoms in current episode (n=157)	6 to 12 weeks	23 (25.8)	12 (17.7)
	> 3 months	31 (34.8)	33 (48.5)
Limitations in activities			
RMDQ (0-23), mean (SD)		14.9 (5.1)	12.4 (5.4)
Psychological variables			
HADS (depression) (0-21), mean (SD)		7.9 (4.3)	5.9 (3.5)
PSEQ‡ (0-60), mean (SD) (n=160)		29.4 (15.0)	34.3 (14.2)
Neurological examination findings			
Presence of muscle weakness§	5/5	68 (73.9)	59 (81.9)
	4/5	22 (23.9)	12 (16.7)
	0 to 3/5	2 (2.2)	1 (1.4)
Presence of either reduced or absent lower limb reflex	None	70 (76.1)	50 (69.4)
	Slightly reduced	4 (4.4)	9 (12.5)
	Significantly reduced	18 (19.6)	13 (18.1)
Reduction or loss of sensation to pin-prick		34 (47.2)	39 (42.4)
Presence of pins and needles		55 (76.4)	67 (72.8)

Baseline characteristics (n=164)*	**†Persistent neuropathic pain (s-LANSS ≥12 at baseline and at four months)**	
	Yes (n=72, 44%)	*No (n=92, 56%)*
Presence of allodynia or hyperalgesia in the leg(s)‖	9 (9.8)	10 (14.0)
Neural tension test** (any positive test)	51 (55.4)	41 (56.9)
Other Neuropathic pain definitions		
Clinical diagnosis of sciatica††	59 (81.9)	79 (85.9)
Neuroimaging		
Evidence of nerve root compression on MRI (n=149)	39 (60.9)	43 (50.6)

Abbreviations: CI, confidence intervals. HADS, Hospital Anxiety and Depression scale. MRI, magnetic resonance imaging. PSEQ, pain self-efficacy questionnaire. RMDQ, Roland Morris Disability Questionnaire leg version. SD, standard deviation.

*Based on data completed by patients who responded to questionnaires at baseline and four months. All figures are for frequency (percentage) unless stated as mean (SD) and the denominator varies for some characteristics varies due to missing or not-applicable cases in which case the denominator is reported in parentheses

† LBLP patients with persistent neuropathic pain: s-LANSS ≥ 12 at baseline and ≥ 12 at four months. Non-persistent neuropathic pain: s-LANSS ≥ 12 at baseline and < 12 at four months.

‡Higher scores on PSEQ reflect stronger self-efficacy beliefs

§ Muscle strength was tested according to a 6-point grading scale where;

No visible flicker of movement or contraction

Flicker of movement

Full active movement with gravity counterbalanced

Full active movement against gravity but not applied resistance

Full active movement against gravity and some applied resistance

Full active movement against gravity and strong resistance

‖ Hyperalgesia is an increased pain response to painful stimuli. Allodynia is pain response to non-painful stimuli (for example, brush strokes)

** Neural tension tests; straight leg raise, femoral stretch and slump test.

†† LBLP patients with a clinical diagnosis of sciatica are described as having “possible” neuropathic pain

8.5.1.2 Persistent neuropathic pain based on a clinical diagnosis of sciatica

In total, 41% (125 out of 301) of patients with neuropathic pain (based on a clinical diagnosis of sciatica) had persistent neuropathic pain at four months. Table 8.4 summarises the baseline characteristics of LBLP patients with and without persistent neuropathic pain defined in this way. Patients with persistent neuropathic pain had higher mean back pain intensity (using NRS 0 to 10, 5.6 (1.5)) compared to those with non-persistent neuropathic pain (4.9 (1.6)), higher mean leg pain intensity (using NRS 0 to 10, 6.3 (2.2) vs 5.2 (2.3)) and higher mean leg, LBLP-related disability scores (using RMDQ 0 to 23, 13.5 (5.4) vs 11.7 (5.8)), a higher proportion of patients with leg pain duration in the current episode of longer than three months (51 (42.2%) vs 50 (28.6%)) and lower mean pain self-efficacy (using PSEQ 0 to 60, 32.2 (14.9) vs 36.7 (14.4)).

Table 8.4 Baseline characteristics of patients with and without persistent neuropathic pain (based on a clinical diagnosis of sciatica)

Baseline characteristics (n=307)*	**†Persistent neuropathic pain (Clinical diagnosis of sciatica and pain below the knee at four months)**	
	Yes (n=125, 41%)	*No (n=182, 59%)*
Sociodemographic characteristics		
Female	88 (70.4)	100 (55.0)
Age, mean (SD)	55.7 (13.6)	53.8 (12.5)

Baseline characteristics (n=307)*		**†Persistent neuropathic pain (Clinical diagnosis of sciatica and pain below the knee at four months)**	
		Yes (n=125, 41%)	*No (n=182, 59%)*
Socio-economic status (n=297)	Higher managerial, administrative and professional occupations	26 (21.9)	39 (21.9)
	Intermediate occupations	31 (26.1)	49 (27.5)
	Routine and manual occupations, never worked and long-term unemployed	62 (52.1)	90 (50.6)
Pain characteristics			
Leg pain intensity (0-10), mean (SD) (n=294)		6.3 (2.2)	5.2 (2.3)
Back pain intensity (0-10), mean (SD) (n=304)		5.6 (1.5)	4.9 (1.6)
Pain below the knee		120 (96.0)	143 (78.6)
Leg pain worse than back pain (n=306)		50 (40.0)	76 (42.0)
Duration of back pain symptoms in current episode (n=306)	< 6 weeks	44 (35.5)	77 (42.3)
	6 to 12 weeks	26 (21.0)	40 (22.0)
	> 3 months	54 (43.6)	65 (35.7)
	< 6 weeks	41 (33.9)	84 (48.0)
	6 to 12 weeks	29 (24.0)	41 (23.4)

Baseline characteristics (n=307)*		**†Persistent neuropathic pain (Clinical diagnosis of sciatica and pain below the knee at four months)**	
		Yes (n=125, 41%)	*No (n=182, 59%)*
Duration of leg pain symptoms in current episode (n=296)	> 3 months	51 (42.2)	50 (28.6)
Limitations in activities			
RMDQ (0-23), mean (SD)		13.5 (5.4)	11.7 (5.8)
Psychological variables			
HADS (depression) (0-21), mean (SD)		6.3 (4.0)	5.9 (3.9)
PSEQ‡ (0-60), mean (SD) (n=300)		32.2 (14.9)	36.7 (14.4)
Neurological examination findings			
Presence of muscle weakness§	5/5	90 (72.0)	143 (78.6)
	4/5	27 (21.6)	36 (19.8)
	0 to 3/5	8 (6.4)	3 (1.7)
Presence of either reduced or absent lower limb reflex	None	100 (80.0)	134 (73.6)
	Slightly reduced	11 (8.8)	9 (5.0)
	Significantly reduced	14 (12.2)	39 (21.4)
Reduction or loss of sensation to pin-prick		64 (51.2)	82 (45.1)
Presence of pins and needles		77 (61.6)	99 (54.4)

Baseline characteristics (n=307)*	**†Persistent neuropathic pain (Clinical diagnosis of sciatica and pain below the knee at four months)**	
	Yes *(n=125, 41%)*	*No* *(n=182, 59%)*
Presence of allodynia or hyperalgesia in the leg(s)‖	11 (8.8)	14 (7.7)
Neural tension test** (any positive test)	79 (63.2)	128 (70.3)
Other Neuropathic pain definitions		
s-LANSS ≥ 12 †† (n=305)	66 (53.7)	83 (45.6)
Neuroimaging		
Evidence of nerve root compression on MRI (n=286)	77 (67.0)	104 (60.8)

Abbreviations: CI, confidence intervals. HADS, Hospital Anxiety and Depression scale. MRI, magnetic resonance imaging. PSEQ, pain self-efficacy questionnaire. RMDQ, Roland Morris Disability Questionnaire (RMDQ) leg version. SD, standard deviation.

* Based on data completed by patients who responded to questionnaires at baseline and four months. All figures are for frequency (percentage) unless stated as mean (SD) and the denominator varies for some characteristics varies due to missing or not-applicable cases in which case the denominator is reported in parentheses.

† LBLP patients with persistent neuropathic pain based on sciatica: clinical diagnosis of sciatica at baseline and pain below the knee at four months. Non-persistent neuropathic pain: clinical diagnosis of sciatica at baseline with no pain below the knee at four months.

‡Higher scores on PSEQ reflect stronger self-efficacy beliefs

§ Muscle strength was tested according to a 6-point grading scale where;
No visible flicker of movement or contraction
Flicker of movement
Full active movement with gravity counterbalanced
Full active movement against gravity but not applied resistance
Full active movement against gravity and some applied resistance
Full active movement against gravity and strong resistance

‖ Hyperalgesia is an increased pain response to painful stimuli. Allodynia is pain response to non-painful stimuli (for example, brush strokes).

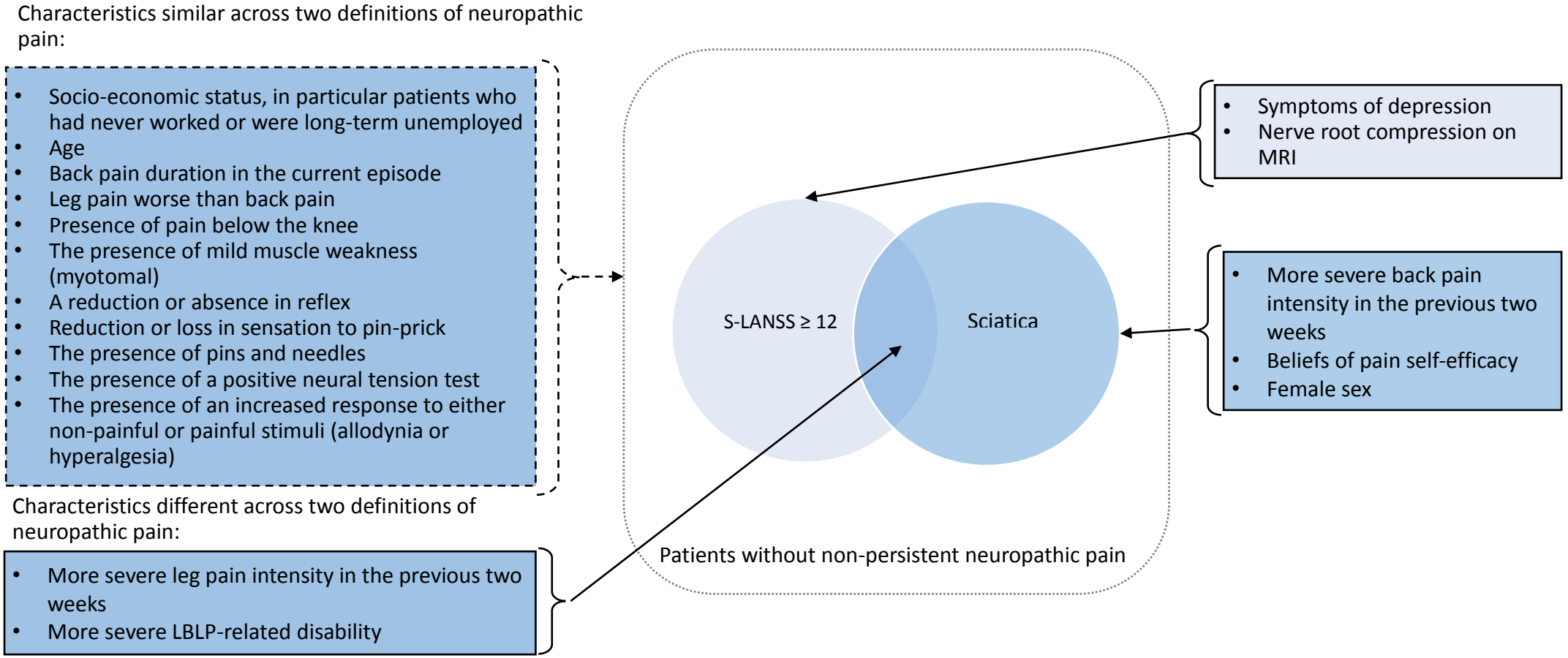
** Neural tension tests; straight leg raise, femoral stretch and slump test.

†† LBLP patients with an s-LANSS score of 12 or greater are described as having “possible” neuropathic pain

8.5.1.3 Comparison of baseline characteristics across two definitions of persistent neuropathic pain

Leg pain intensity and LBLP-related disability were consistently worse for patients with persistent neuropathic pain compared to those without across the two definitions. Of the six items from the neurological examination, all were similar for patients with persistent neuropathic pain compared to those with non-persistent neuropathic pain across both definitions of persistent neuropathic pain. Figure 8.1 summarises the characteristics that were similar for patients with and without persistent neuropathic pain consistently across two definitions.

Figure 8.1 Summary of baseline characteristics for LBLP patients with and without persistent neuropathic pain across two definitions.



Abbreviations: MRI, magnetic resonance imaging. s-LANSS, self-report version of the Leeds Assessment of Neurological symptoms and signs
LBLP patients with persistent neuropathic pain based on: 1) s-LANSS, s-LANSS ≥ 12 at baseline and ≥ 12 at four months. Non-persistent neuropathic pain: s-LANSS ≥ 12 at baseline and < 12 at four months, 2) sciatica, clinical diagnosis of sciatica at baseline and pain below the knee at four months. Non-persistent neuropathic pain: clinical diagnosis of sciatica at baseline with no pain below the knee at four months.

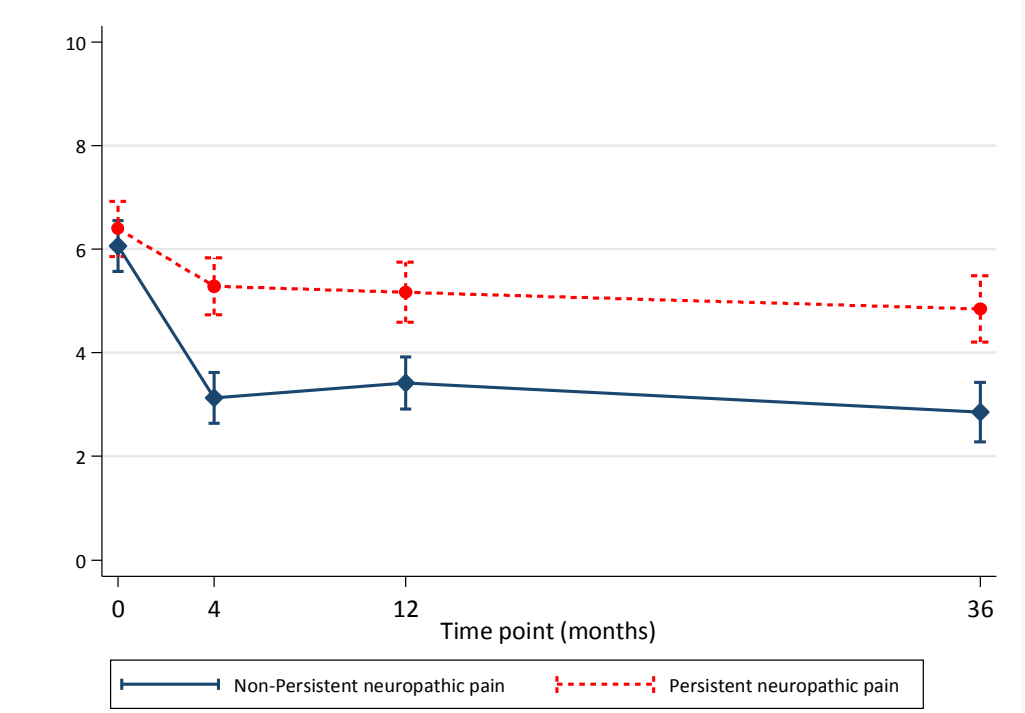
8.5.2 Clinical course

8.5.2.1 Persistent neuropathic pain based on s-LANSS

Mean (unadjusted) pain intensity of patients with persistent neuropathic pain was higher at baseline, four months (6.4 v 3.2), twelve months (5.0 v 3.0) and at three years (4.8 v 2.9), compared to those with non-persistent neuropathic pain. When baseline pain intensity scores were adjusted to account for variability of scores, patients with persistent neuropathic pain had significantly higher scores at each of the three follow-up points, compared to those without. Mean (unadjusted) disability scores of patients with persistent neuropathic pain was higher at baseline, four months (12.7 v 6.7), twelve months (13.0 v 7.5) and at three years (8.8 v 5.8). When baseline disability scores were adjusted patients with persistent neuropathic pain had significantly higher scores at four months, but not twelve months or three years. See Box 8.2 and Box 8.3 for a summary of the clinical course of patients with and without persistent neuropathic pain based on s-LANSS.

Box 8.2 Three year clinical course (pain intensity) of patients with and without persistent neuropathic pain (based on s-LANSS) at four months*

Unadjusted clinical course



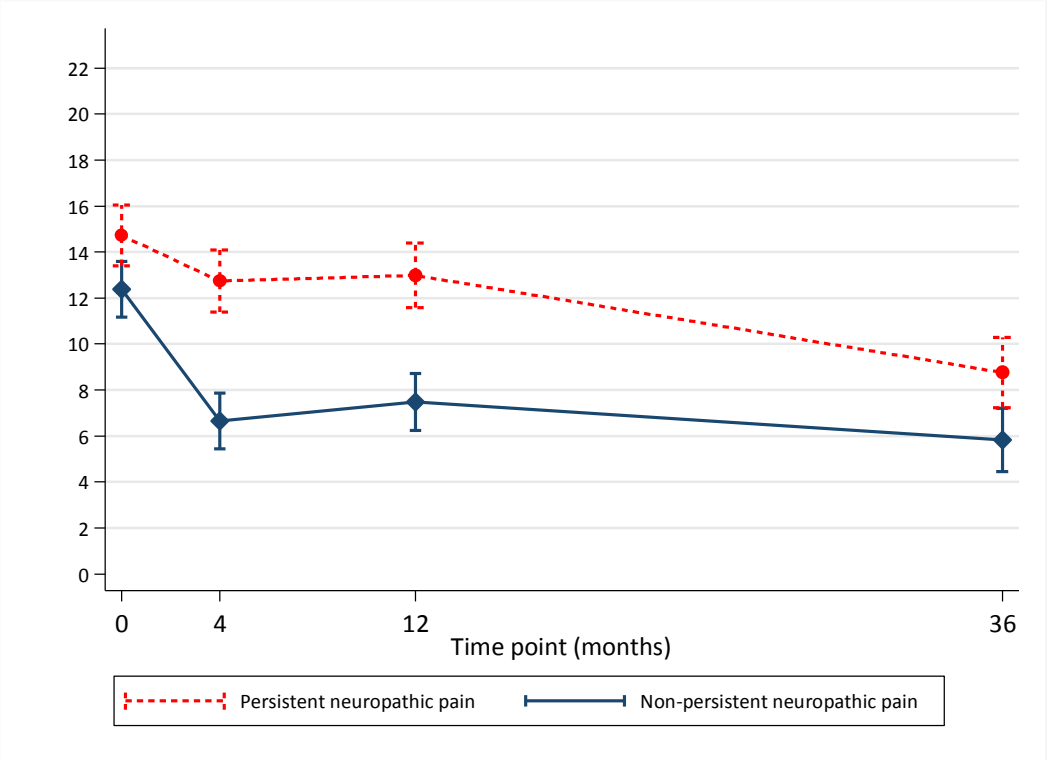
Clinical course adjusted for baseline pain score

Follow-up point	Persistent neuropathic pain at four months‡		p
	Yes	*No*	
Baseline	6.17 (5.8 to 6.6)	6.17 (5.8 to 6.6)	-
4 months	5.2 (4.7 to 5.6)	3.2 (2.8 to 3.6)	0.02
12 months	5.1 (4.6 to 5.5)	3.5 (3.0 to 3.9)	0.002
3 years	4.7 (4.2 to 5.3)	2.9 (2.4 to 3.6)	0.002

Abbreviations: NRS, numerical rating scale. s-LANSS, self-report version of the Leeds Assessment of Neuropathic Symptoms and Signs neuropathic pain scale. *Highest of leg or back pain intensity (mean of 3 NRS, 0-10)). ‡ Based on analysis of LBLP patients with neuropathic pain (s-LANSS ≥ 12) at baseline. Persistent neuropathic pain: s-LANSS ≥ 12 at four months. Non-persistent pain: s-LANSS < 12 at four months
95% confidence intervals are shown in parentheses

Box 8.3 Three year clinical course (leg and back-related disability) of patients with and without persistent neuropathic pain (based on s-LANSS) at four months*

Unadjusted clinical course



Clinical course adjusted for baseline RMDQ score

Follow-up point	**Persistent neuropathic pain at four months‡**		**p**
	Yes	*No*	
Baseline	13.3 (12.4 to 14.2)	13.3 (12.4 to 14.2)	-
4 months	11.8 (10.7 to 12.8)	7.2 (6.3 to 8.2)	0.02
12 months	11.9 (10.8 to 13.0)	8.2 (7.2 to 9.1)	0.07
3 years	7.9 (6.7 to 9.2)	5.9 (4.8 to 7.1)	0.13

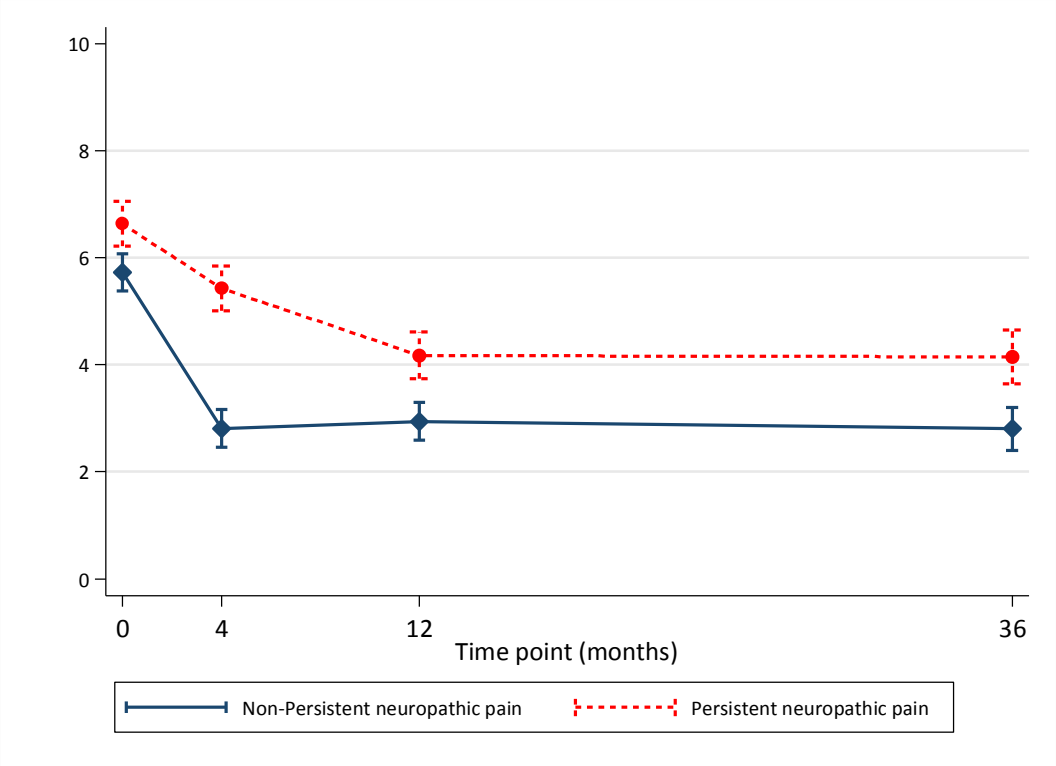
Abbreviations: NRS, numerical rating scale. RMDQ, Roland Morris Disability Questionnaire leg version. s-LANSS, self-report version of the Leeds Assessment of Neuropathic Symptoms and Signs neuropathic pain scale.‡ Based on analysis of LBLP patients with neuropathic pain (s-LANSS ≥ 12) at baseline. Persistent neuropathic pain: s-LANSS ≥ 12 at four months. Non-persistent pain: s-LANSS < 12 at four months
95% confidence intervals are shown in parentheses

8.5.2.2 Persistent neuropathic pain based on a clinical diagnosis of sciatica

Mean (unadjusted) pain intensity of patients with persistent neuropathic pain was higher at baseline, four months (5.4 v 2.8), twelve months (4.2 v 2.9) and at three years (4.2 v 2.8), compared to those with non-persistent neuropathic pain. When baseline pain intensity scores were adjusted to account for variability of scores at baseline, patients with persistent neuropathic pain had significantly higher scores at all three time points. Mean (unadjusted) disability scores of patients with persistent neuropathic pain were higher at baseline, four months (11.8 v 6.0), twelve months (10.2 v 6.4) and at three years (7.8 v 5.0), compared to those with non-persistent neuropathic pain; this was also the case for mean adjusted disability scores at all three follow-up points. See Box 8.4 and Box 8.5 for a summary of the clinical course of patients with and without persistent neuropathic pain based on sciatica.

Box 8.4 Three year clinical course (pain intensity) of patients with and without persistent neuropathic pain (based on a clinical diagnosis of sciatica) at four months*

Unadjusted clinical course



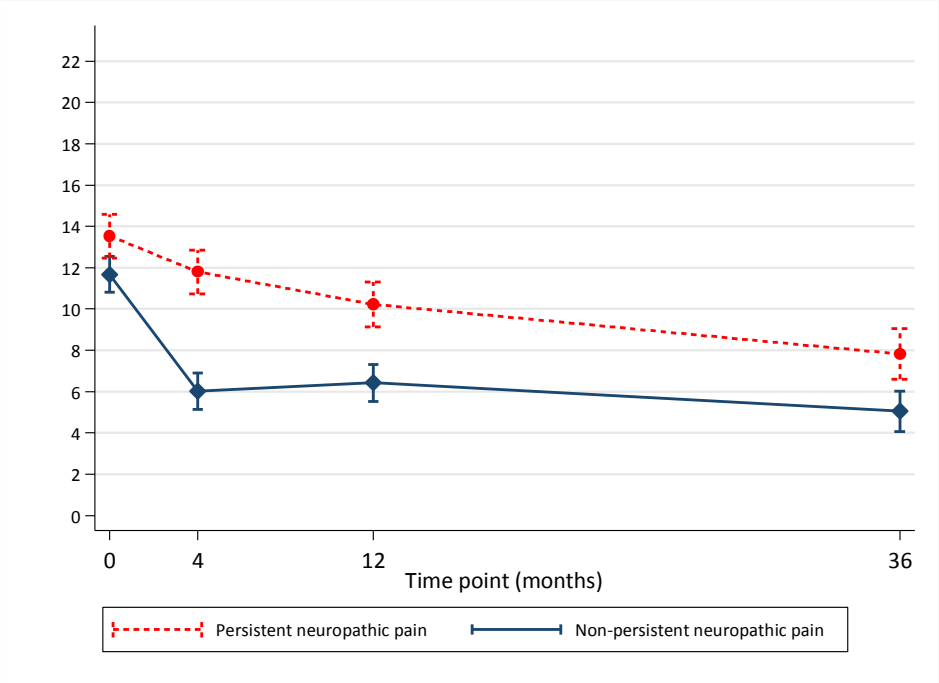
Clinical course adjusted for baseline pain score

Follow-up point	Persistent neuropathic pain at four months‡		p
	Yes	*No*	
Baseline	6.1 (5.8, 6.4)	6.1 (5.8, 6.4)	-
4 months	5.1 (4.8, 5.5)	3.0 (2.7, 3.3)	<0.001
12 months	3.9 (3.5, 4.3)	3.1 (2.8, 3.4)	0.006
3 years	3.9 (3.4)	2.9 (2.6, 3.3)	0.002

Abbreviations: NRS, numerical rating scale.*Highest of leg or back pain intensity (mean of 3 NRS, 0-10)).
‡ Based on analysis of LBLP patients with neuropathic pain (clinical diagnosis of sciatica) at baseline. Persistent neuropathic pain: presence of pain below the knee at four months. Non-persistent pain: absence of pain below the knee at four months. 95% confidence intervals are shown in parentheses

Box 8.5 Three year clinical course (leg and back-related disability) of patients with and without persistent neuropathic pain (based on a clinical diagnosis of sciatica) at four months*

Unadjusted clinical course



Clinical course adjusted for baseline RMDQ score

Follow-up point	Persistent neuropathic pain at four months‡		p
	Yes	*No*	
Baseline	12.3 (11.6, 13.0)	12.3 (11.6, 13.0)	-
4 months	11.1 (10.2, 11.9)	6.4 (5.7, 7.1)	<0.001
12 months	9.5 (8.6, 10.3)	6.8 (6.1, 7.5)	0.007
3 years	7.1 (6.2, 8.1)	5.1 (4.3, 5.9)	0.001

Abbreviations: NRS, numerical rating scale. RMDQ, Roland Morris Disability Questionnaire leg version.
‡ Based on analysis of LBLP patients with neuropathic pain (clinical diagnosis of sciatica) at baseline.
Persistent neuropathic pain: presence of pain below the knee at four months. Non-persistent pain: absence of pain below the knee at four months. 95% confidence intervals are shown in parentheses.

8.5.2.3 Comparison of clinical course across two definitions of persistent neuropathic pain

Using both definitions of persistent neuropathic pain, the clinical course of patients was consistently worse in terms of pain intensity compared to those with non-persistent neuropathic pain at four months, twelve months and three years, using scores adjusted for baseline variability. The clinical course of patients with persistent neuropathic pain, adjusted for baseline variability in individual LBLP-related disability (using RMDQ) scores was worse at twelve months and three years compared to those without for one definition of persistent neuropathic pain, and at four months for both definitions of neuropathic pain. Mean adjusted and unadjusted pain intensity were higher for patients with persistent neuropathic pain based on s-LANSS at each of the three follow-up points compared to those with persistent neuropathic pain based on sciatica, this was also the case for disability scores.

8.5.3 Identification of potential prognostic factors

8.5.3.1 Persistent neuropathic pain based on s-LANSS

Table 8.5 reports OR (and 95% CI) for univariable associations between each of the factors identified as having potential prognostic value in persistent neuropathic pain. Only pain self-efficacy was statistically significantly associated with persistent neuropathic pain, for every one unit reduction in pain self-efficacy score (using PSEQ), the odds of having persistent neuropathic pain increased by 2% (OR 0.98, CI 0.96 to 0.998). Evidence of nerve root compression on MRI was not statistically associated

with persistent neuropathic pain (p=0.24) but was carried forward to the multivariable model.

Table 8.5 Univariable associations between potential prognostic factors and persistent neuropathic pain at four months (based on s-LANSS)

Prognostic factor		***Persistent neuropathic pain (s-LANSS ≥12 at baseline and at four months), OR (95% CI)**
Age		1.01 (0.99, 1.03)
Female sex		0.85 (0.47, 1.52)
Socio-economic status	Higher managerial, administrative and professional occupations	1
	Intermediate occupations	0.99 (0.39, 2.49)
	Routine and manual occupations, never worked and long-term unemployed	1.12 (0.48, 2.60)
Leg pain intensity (0-10)		1.10 (0.97, 1.25)
Pain below the knee		1.22 (0.60, 2.50)
Duration of leg pain symptoms in current episode	< 6 weeks	1
	6 to 12 weeks	0.82 (0.39, 1.74)
	> 3 months	1.21 (0.65, 2.28)
Pain self-efficacy using PSEQ‡ (0-60)		0.98 (0.96, 0.998)

Reduction or loss of sensation to pin-prick	1.06 (0.61, 1.83)
Presence of pins and needles	1.26 (0.68, 2.33)
Clinical diagnosis of sciatica††	0.75 (0.38, 1.49)
Evidence of nerve root compression on MRI	1.40 (0.80, 2.45)

Abbreviations: CI, confidence intervals. MRI, magnetic resonance imaging. PSEQ, pain self-efficacy questionnaire.
Results underlined highlight significance level p<0.05
Based on analysis of LBLP patients with neuropathic pain (s-LANSS ≥ 12) at baseline. Persistent neuropathic pain: s-LANSS ≥ 12 at four months. Non-persistent pain: s-LANSS < 12 at four months
‡Higher scores on PSEQ reflect stronger self-efficacy beliefs
† † LBLP patients with a clinical diagnosis of sciatica are described as having "possible" neuropathic pain

8.5.3.2 Persistent neuropathic pain based on a clinical diagnosis of sciatica

The univariable associations between each of the factors identified as having potential prognostic value in persistent neuropathic pain is summarised in Table 8.6. Four potential factors were significantly associated with persistent neuropathic pain; female sex (OR 1.95, CI 1.20 to 3.16); leg pain duration greater than three months (OR 1.91, CI 1.12 to 3.26); leg pain intensity, for every one unit increase in leg pain intensity score, the odds of having persistent neuropathic pain increased by 21% (OR 1.21, CI 1.09 to 1.35); pain self-efficacy, for every one unit reduction in PSEQ score, the odds of having persistent neuropathic pain increased by 2% (OR 0.98, CI 0.96 to 0.99).

Table 8.6. Univariable associations between potential prognostic factors and persistent neuropathic pain at four months (based on a clinical diagnosis of sciatica)

Prognostic factor		***Persistent neuropathic pain (Clinical diagnosis of sciatica and pain below the knee at four months) OR (95% CI)**
Age		1.01 (0.99, 1.03)
Female sex		1.95 (1.20, 3.16)
Socio-economic status	Higher managerial, administrative and professional occupations	1
	Intermediate occupations	0.96 (0.49, 1.87)
	Routine and manual occupations, never worked and long-term unemployed	1.05 (0.58, 1.89)
Leg pain intensity (0-10)		1.21 (1.09, 1.35)
Duration of leg pain symptoms in current episode	< 6 weeks	1
	6 to 12 weeks	1.38 (0.76, 2.52)
	> 3 months	1.91 (1.12, 3.26)
PSEQ† (0-60)		0.98 (0.96, 0.99)
Reduction or loss of sensation to pin-prick		1.28 (0.81, 2.02)
Presence of pins and needles		1.34 (0.85, 2.13)
s-LANSS ≥ 12 ‡		1.45 (0.92, 2.30)

Evidence of nerve root compression on MRI	1.27 (0.78, 2.08)

Abbreviations: CI, confidence intervals. OR, odds ratio. PSEQ, pain self-efficacy questionnaire.
Results underlined highlight significance level p<0.05
* Showing results for 60 multiply-imputed datasets, based on analysis of LBLP patients with neuropathic pain (clinical diagnosis of sciatica) at baseline. Persistent neuropathic pain: presence of pain below the knee at 4 months. Non-persistent pain: absence of pain below the knee at 4 months.
† Higher scores on PSEQ reflect stronger self-efficacy beliefs
‡ LBLP patients with s-LANSS ≥ 12 are described as having "possible" neuropathic

The following section reports on the prognostic value of pain self-efficacy and evidence of nerve root compression on MRI.

8.5.4 Prognostic value of selected factors

8.5.4.1 Prediction of persistent neuropathic pain based on s-LANSS

Neither evidence of nerve root compression on MRI nor pain self-efficacy were significantly associated with persistent neuropathic pain when included in the model with age, sex, leg pain intensity, duration of current leg pain. Results are presented in Table 8.7.

Table 8.7 Multivariable associations between potential prognostic factors and persistent neuropathic pain (based on s-LANSS) at four months

Prognostic factor		*Persistent neuropathic pain (s-LANSS ≥12 at baseline and at four months), OR (95% CI)
Age		1.01 (0.98, 1.03)
Female sex		0.94 (0.50, 1.76)
Leg pain intensity (0-10)		1.02 (0.88, 1.19)
Duration of leg pain symptoms in current episode	< 6 weeks	1
	6 to 12 weeks	0.82 (0.37, 1.78)
	> 3 months	1.12 (0.58, 2.18)
Pain self-efficacy using PSEQ‡ (0-60)		0.98 (0.96, 1.00)
Evidence of nerve root compression on MRI		0.80 (0.15, 4.35)

Abbreviations: CI, confidence intervals. PSEQ, pain self-efficacy questionnaire.
* Showing results for 60 multiply-imputed datasets, based on analysis of LBLP patients with neuropathic pain (s-LANSS ≥ 12) at baseline. Persistent neuropathic pain: s-LANSS ≥ 12 at four months. Non-persistent pain: s-LANSS < 12 at four months
‡Higher scores on PSEQ reflect stronger self-efficacy beliefs

8.5.4.2 Prediction of persistent neuropathic pain based on a clinical diagnosis of sciatica

When entered into a multivariable regression model, neither evidence of nerve root compression on MRI nor pain self-efficacy were significantly associated with persistent neuropathic pain. Leg pain intensity and female sex were associated with persistent neuropathic pain, summarised in Table 8.8. The odds of having persistent neuropathic pain was twice as high (OR 2.09, CI 1.24 to 3.53) for female patients compared to male

patients. For every one unit increase in leg pain intensity, the odds of having persistent neuropathic pain increased by 13% (OR 1.13, CI 1.01 to 1.28).

Table 8.8 Multivariable associations between potential prognostic factors and persistent neuropathic pain (based on a clinical diagnosis of sciatica) at four months

Prognostic factor		**[*] Persistent neuropathic pain (Clinical diagnosis of sciatica and pain below the knee at four months), OR (95% CI)**
Age		1.01 (0.99, 1.03)
Female sex		2.09 (1.24, 3.53)
Leg pain intensity (0-10)		1.13 (1.01, 1.28)
Duration of leg pain symptoms in current episode	< 6 weeks	1
	6 to 12 weeks	1.47 (0.77, 2.78)
	> 3 months	1.59 (0.91, 2.79)
PSEQ[†] (0-60)		0.98 (0.97, 1.00)
Evidence of nerve root compression on MRI		1.26 (0.74, 2.15)

Abbreviations: CI, confidence intervals. OR, odds ratio. PSEQ, pain self-efficacy questionnaire.
Results underlined highlight significance level p<0.05
[*] Showing results for 60 multiply-imputed datasets, based on analysis of LBLP patients with neuropathic pain (clinical diagnosis of sciatica) at baseline. Persistent neuropathic pain: presence of pain below the knee at 4 months. Non-persistent pain: absence of pain below the knee at 4 months.
[†]Higher scores on PSEQ reflect stronger self-efficacy beliefs

8.5.3.3 Prognostic value of factors across two definitions of persistent neuropathic pain

In multivariable analysis of potential factors, neither evidence of nerve root compression on MRI nor pain self-efficacy was associated with persistent neuropathic pain. Female sex and leg pain intensity were associated with persistent neuropathic pain based on one definition (clinical diagnosis of sciatica).

8.6 Discussion

The research in this chapter reports on the characteristics and prognosis of patients with persistent neuropathic pain and highlights exploratory prognostic factor research for two definitions of neuropathic pain. This section summarises the key findings, makes comparisons with existing literature, and following a section on the strengths and limitations of the research, considers the implications for clinical practice and research before drawing key conclusions.

8.6.1 Baseline characteristics and clinical course

Approximately four out of ten patients with neuropathic pain at baseline had persistent neuropathic pain at four months, irrespective of definition. Across both definitions, patients with persistent neuropathic pain presented with more severe leg pain intensity and leg and back pain-related disability at baseline. It was surprising that all of the six items from the neurological examination were similar for patients with and without persistent neuropathic pain across both definitions. This suggests that items from the neurological examination may be indicative of mechanisms underlying neuropathic pain when patients present at baseline but the same mechanisms may not explain persistent neuropathic pain.

The clinical course in patients with persistent neuropathic pain was characterised by a gradual improvement of pain over short term (four months), intermediate (twelve months) and long-term (three years) follow up which is distinct to the broader group of patients either with or without neuropathic pain whose course rapidly improved by four months (the reader is referred to Chapter 6 for a detailed report on the clinical

course of patients with and without neuropathic pain). However the clinical course of LBLP patients with persistent neuropathic pain in terms of pain intensity seemed worse at each of the three follow-up points compared to those with non-persistent neuropathic pain, consistently for both definitions of persistent neuropathic pain, but less consistently in terms of LBLP-related disability. In part this may be due to small numbers in the group of patients with persistent neuropathic pain based on s-LANSS. Understanding the factors that predict which patients with neuropathic pain are likely to have persistent neuropathic pain is important since their likely future course will be worse than those patients who do not have persistent neuropathic pain. The following section discusses the findings from the exploratory prognostic factor analyses.

8.6.2 Exploratory prognostic factor research

The findings from the exploratory prognostic factor research in LBLP patients with neuropathic pain at baseline highlights the prognostic value of a small number of characteristics in this patient group. This type of research exploring the potential prognostic value of factors is important to inform further research that may develop and validate prognostic models that help identify those patients with neuropathic pain who are likely to have a poor outcome (Riley et al. 2013). In the current analyses only one factor, pain self-efficacy, was significantly associated with persistent neuropathic pain in univariable regression models, but lost significance when entered into a multivariable model with other potential factors considered to be clinically important in this patient population. This finding was consistent across both definitions of persistent neuropathic pain. In the multivariable model, female sex and higher leg pain

intensity remained significantly associated with persistent neuropathic pain. However, this finding was observed using one (sciatica), not both, definitions of persistent neuropathic pain.

The finding that higher leg pain intensity was associated with one definition of persistent neuropathic pain is perhaps not surprising since in a systematic review of patients with neuropathic pain (Boogaard et al. 2015) higher pain intensity predicted poor outcomes across several neuropathic pain conditions. In non-surgically treated sciatica patients (Verwoerd et al. 2013), higher leg pain intensity predicted poor outcomes, and in broader LBP populations in primary care pain severity was found to be associated with poorer outcomes (Dunn et al. 2011). Female sex in this research was associated with persistent neuropathic pain (sciatica) which is also comparable to previous research (Peul et al. 2008) in patients with sciatica plus evidence of nerve root compression. Sex hormones probably have an effect on the underlying mechanisms of pain and may contribute, in part, to sex differences seen in this research (Picavet 2010). However, it was unexpected that none of the potential prognostic factors selected were significantly associated with persistent neuropathic pain based on s-LANSS, this highlights the challenge in predicting which patients with neuropathic pain will have persistent neuropathic pain. A discussion follows on the complexities of prognostic research in patients with neuropathic pain, including consideration of the selection of potential prognostic factors and the definitions of persistent neuropathic pain in this research.

8.6.2.1 Potential prognostic factors

In this research, the presence of pins and needles in the painful leg (a positive neuropathic sign) and the reduction or loss of sensation in the painful leg (a negative neuropathic sign) were identified as potential prognostic factors and there is some consensus amongst experts that these factors may predict poor outcomes in patients with neuropathic pain (Boogaard et al. 2011). However, in this research neither the presence of pins and needles in the painful leg nor the reduction or loss of sensation in the painful leg were associated with persistent neuropathic pain. The presence of pins and needles may be a sign of underlying pathophysiology such as demyelination and is thought to be an important positive sign of neuropathic pain, it is biologically plausible but there is an absence of evidence in the literature that the presence of pins and needles could be a potential prognostic factor of persistent neuropathic pain (Boogaard et al. 2015).

A reduction or loss of sensation was not associated with persistent neuropathic pain in this research, a finding that is consistent with previous prognosis research (Martinez et al. 2012) investigating patients with persistent neuropathic pain (based on the DN4) three months after surgery (in which post-surgical pain is assumed to be a neuropathic pain condition). The results of the current research suggest that although negative signs characterise neuropathic pain conditions, a reduction or loss of sensation may not predict persistent neuropathic pain.

The presence of an increased pain response is a positive sign of neuropathic pain and may predict persistent neuropathic pain (based on DN4) (Martinez et al. 2012). The

reason not to consider an increased pain response as a potential prognostic factor in the current analyses was methodological. Firstly, it was thought important to select strong prognostic factors for this research, where the strength of a factor is a function of the association between factor and outcome and secondly, on how common the factor occurs in a population (Steyerberg 2009). In this research with LBLP patients, there was some evidence that an increased pain response was associated with neuropathic pain (based on one definition) but it was not a common finding in this patient population (see Chapter 5 for a detailed report of the baseline characteristics of LBLP patients with and without neuropathic pain). Secondly, a limited number of factors could be selected due to the small numbers and priority was given to stronger predictors. Section 8.6.3 highlights the small sample size as a limitation of this research. An increased pain response is characteristic of neuropathic pain but it is not exclusive to neuropathic pain conditions and is likely to be a sign of central sensitisation. Previous chapters highlighted evidence that suggests the underlying pain mechanisms of neuropathic pain based on s-LANSS may in part be due to central sensitisation and there is considerable interest in the role of an increased pain response. Future empirical prognostic research with this patient population that investigates whether an increased pain response is associated with persistent neuropathic pain would be of value, but the challenge is the very low prevalence of this clinical sign in this population. It is likely that evidence of nerve root compression on MRI in part explains peripheral mechanisms of neuropathic pain in this patient population whilst other mechanisms may contribute to ongoing persistence. Other mechanisms and in particular inflammatory mechanisms may be particularly important

(Hung et al. 2017, Schmid et al. 2013) in persistent neuropathic pain (the reader is referred to Chapter 1, section 1.14 for a report on pain arising from inflammation). Inflammation may occur systemically because of chronic disease, obesity, medication use, smoking and heavy alcohol consumption (Hung et al. 2017) but in LBLP patients inflammation may also be dependent on symptom severity (Wang et al. 2016). In the future, understanding the role of inflammatory mechanisms underlying LBLP patients with and without neuropathic pain may provide greater explanation of the mechanisms underlying LBLP and provide a therapeutic target in this patient population (Hung et al. 2017).

Over recent decades there has been increasing use of QST to understand the somatosensory function in patients with neuropathic pain. There is a paucity of evidence to help researchers or clinicians understand whether responses to QST in LBLP populations have prognostic value (Marcuzzi et al. 2016). In this research, prognostic factors selected from a large number of self-reported variables and routine clinical examination items has not resulted in clear identification of factors significantly associated with persistent neuropathic pain in patients initially presenting with neuropathic pain. It is possible that additional assessment of the prognostic value of QST variables in this patient population might be helpful. Overall, the results of the current research highlight that items from routine neurological examination, including MRI, deemed important for defining cases of neuropathic pain at baseline did not explain the presence of persistent neuropathic pain at four months.

8.6.2.2 Definitions of persistent neuropathic pain

In the current research, two definitions of persistent neuropathic pain based on either s-LANSS or clinical diagnosis of sciatica were used. In the absence of clinical examination data at four months the presence of pain below the knee was used as a proxy for sciatica at four months. This research is the first to explore prognostic factors using a prospective cohort of patients, the use of two definitions of persistent neuropathic pain allowed for comparisons to be made and conclusions to be drawn. The presence of pain below the knee is an acceptable proxy for sciatica but may over-identify cases (Konstantinou et al. 2012c) and may have led to an over estimation of persistent neuropathic pain at four months. It is likely the sciatica prevalence in this patient group would have been lower than 41%, if based on clinical examination.

Previous chapters have highlighted similarities but also distinct differences in baseline characteristics and clinical course in patients with neuropathic pain across the two approaches. It is plausible that prognostic factors thought to predict persistent neuropathic pain based on s-LANSS may not explain cases of persistent neuropathic pain based on sciatica. Further exploratory prognostic research may investigate whether there are factors common and/or unique to distinct definitions of persistent neuropathic pain in this patient population.

A discussion follows on the strengths and limitations of this research, followed by consideration of the implications for future prognostic factor research in this patient population.

8.6.3 Strengths and limitations

The main strength of this research is the prospective cohort design, use of multiple imputation to account for missing data and use of more than one definition of persistent neuropathic pain. A further strength of this analysis is the approach to selecting potential prognostic factors from the available dataset, chosen as they were thought to be clinically potential important factors for poor prognosis in neuropathic pain conditions and separately in LBP populations. This approach of factor selection was chosen over variable selection based on univariable statistical significance, and it is thought to reduce potential bias and over-optimism of potential prognostic effects (Sun et al. 1996).

The main limitation is the small number of both the outcome, persistent neuropathic pain (n=72) and a relatively small sample size (n=164) for patients with persistent neuropathic pain based on s-LANSS. This was an important consideration when interpreting differences and similarities in baseline characteristics, resulted in large confidence intervals around point estimates of pain intensity and LBLP-related disability when comparing clinical course and in few prognostic factors being able to be selected for the exploratory prognostic factor research. The number of factors selected for the multivariable model was thought to be conservative (a maximum of seven factors) but this may not have been conservative enough (van Smeden et al. 2016). This research was based on secondary analysis of a prospective cohort and future studies of prognostic factors in this patient population would need larger sample sizes than those in this study to provide more robust evidence about prognostic factors.

A second limitation may have been the method of selecting potential prognostic factors for this research. In part, potential factors were selected on the finding of consistent associations with neuropathic pain across three definitions in LBLP patients, hence a few prognostic factors were identified. Further and larger scale prognostic factor research is required to address these limitations. A third limitation is the use of a proxy for sciatica case definition at follow-up.

8.6.4 Implications for clinical practice and research

The current research highlights that the clinical course of a sub-group of LBLP patients with persistent neuropathic pain is not favourable at short term, intermediate and long-term follow up compared to those without. This prognostic information is important for clinicians and to patients who continue to consult with neuropathic pain in primary care. Leg pain intensity and female sex may predict those who will have persistent neuropathic pain but this should be interpreted in clinical practice with caution given the exploratory nature of this prognostic factor research.

In terms of implications for research, this sub-group of patients is important because they were identified based on an unfavourable clinical course but this research highlights difficulty not only in predicting which patients have persistent neuropathic pain but also difficulty in defining persistent neuropathic pain. Replication of the analysis completed in this research in a larger sample of patients may shed more light particularly on the factors that predict persistent neuropathic pain, and allow for an investigation of a greater number of potential prognostic factors. Data collected from clinical examination and MRI at baseline and at a subsequent time point would allow

for further investigation of the usefulness of the definition of persistent neuropathic pain in this patient population. Finally, further research exploring the prognostic value of responses to QST or biomarkers of inflammatory mechanisms in this patient population, may add to the understanding of the factors that are associated with persistent neuropathic pain.

8.7 Conclusions

Persistent neuropathic pain affected approximately four out of ten LBLP patients with neuropathic pain who consult in primary care. Baseline leg pain intensity and LBLP-related disability in patients with persistent neuropathic pain were worse compared to those without. Otherwise patients with persistent neuropathic pain were broadly similar and were difficult to distinguish from patients with non-persistent neuropathic pain based on patient profile at baseline. However, patients with persistent neuropathic pain, in terms of pain intensity, were consistently worse off up to three years follow-up compared to those without. Pain self-efficacy was not an independent factor associated with outcome in either of the two definitions of persistent neuropathic pain, neither was evidence of nerve root compression on MRI. There was some evidence that leg pain intensity and female sex were associated with persistent neuropathic pain based on a clinical diagnosis of sciatica and pain below the knee at four months but otherwise it was difficult to predict patients with persistent neuropathic pain four months after their consultation in primary care. The current prognostic research was based on small numbers of patients with persistent neuropathic pain so the findings should be interpreted with caution. Future larger

studies might contribute further to a better understanding of this important patient sub-group with persistent neuropathic pain.

Chapter Nine. Prescribing patterns of pain medications in LBLP patients with neuropathic pain

9.1 Introduction

The research in this chapter describes the patterns of prescribed pain medications, including specific neuropathic pain medication, in LBLP patients with neuropathic pain who consult in primary care. Previous chapters in this thesis highlighted that the clinical course of patients with neuropathic pain at baseline improves rapidly for most by short term (four months) follow up (Chapter 6), but the clinical course of patients in the persistent neuropathic pain sub-group was worse at long term (three years) follow up compared to those without persistent neuropathic pain (Chapter 8). The research in this chapter describes the prescribing patterns of pain medications in this patient population by short term, intermediate and longer term follow-up. It describes the change in pain intensity or LBLP-related disability in those patients who are prescribed neuropathic pain medication compared to those who are not. Finally, the research in this chapter identifies and describes those LBLP patients with refractory neuropathic pain. These patients experience significant, long-term signs and symptoms of neuropathic pain and do not respond to standard treatment such as neuropathic pain medication. The findings are compared to existing literature before considering their clinical and research implications.

9.2 Aims and objectives

9.2.1 Overall aim

To provide estimates and describe prescribing patterns for pain medications in LBLP patients with neuropathic pain who consult in primary care and to estimate the proportion of LBLP patients with refractory neuropathic pain.

9.2.2 Objectives

1. Provide estimates and describe prescribing patterns for pain medications, including specific neuropathic pain medication in LBLP patients with neuropathic pain.
2. Describe the baseline characteristics of LBLP patients with neuropathic pain, and the number of primary care consultations for patients who were prescribed neuropathic pain medication compared to those who were not.
3. Describe the proportion of LBLP patients with neuropathic pain who improve in terms of pain intensity or leg and back pain-related disability.
4. Provide estimates of refractory neuropathic pain in LBLP patients with neuropathic pain consulting in primary care.

9.3 Methods

9.3.1 Study design

The research presented in this chapter is based on secondary analysis of a prospective observational cohort of primary care LBLP patients who consulted with their general practitioner (see Chapter 4 Study design and Methods for a detailed report on the ATLAS study).

9.3.2 Data collection

Data regarding prescribed pain medication were obtained from electronic prescribing and consulting records for consenting patients in the ATLAS study at participating general practices. Prescribing data were obtained for the four month (122 days) period before the date of first attendance at the ATLAS research clinic, and up to the subsequent three years (1464 days). This timescale ensured inclusion of prescribing data for the current episode of back and leg pain (62% to 67% of patients with neuropathic pain (depending on definition) reported the duration of their current episode of leg pain to be less than three months). The analyses in this chapter is based on complete cases.

9.3.2.1 Pain medications

The number of pain medications prescribed to an individual patient during the study period was considered for use in this analysis. Pain medications were then categorised into seven groups based on recommendations from existing literature (Bedson et al. 2013, NICE CG173 2013, Qaseem et al. 2017). See Chapter 4, section 4.9.8.1 (page 134) for a detailed report on the categorisation of pain medication in the research in this chapter, a summary of this is given below in Table 9.1.

Table 9.1 Summary of groups of pain medication in research in Chapter nine

Pain medication group	**Example**
First-line neuropathic pain medication*	Amitriptyline, Duloxetine, Gabapentin or Pregabalin

Pain medication group	Example
Basic analgesia	Paracetamol
Weak to moderate opioids	Co-codamol, Co-dydramol and weak dosages of Codeine or Dihydrocodeine
Strong to very strong opioids	Tramadol ≥50mg, Morphine or Oxycodone
Non-steroidal anti-inflammatory medication	Naproxen or Ibuprofen >400mg
Skeletal muscle relaxants	Diazepam

Abbreviations: mg, milligram
*Tramadol was also categorised into a seventh group of broader neuropathic pain medications (Tramadol, Amitriptyline, Duloxetine, Gabapentin, and Pregabalin)

9.3.3 Definitions of neuropathic pain, refractory neuropathic pain and improvement

As in previous chapters, the research in this chapter defines cases according to three definitions of neuropathic pain and one definition of persistent neuropathic pain (see Chapter 4, section 4.7 (page 118) for a full report on case definitions of neuropathic pain used in this thesis). Two definitions describe “possible” neuropathic pain, based on s-LANSS, and on clinical diagnosis of sciatica; one definition describes “probable” neuropathic pain based on a definition of clinical diagnosis of sciatica with evidence of nerve root compression on MRI. Persistent neuropathic pain was based on s-LANSS at baseline and at four months and describes a sub-group of patients with “possible” persistent neuropathic pain.

Refractory neuropathic pain in this research was based on the definition described by Smith et al. (2012a). LBLP patients with persistent neuropathic pain (s-LANSS score of 12 or greater at baseline and at four months) who continue to experience leg pain intensity levels of 5 or more (from the mean of three 0-10 NRSs) or less than 30% reduction in leg and back pain-related disability (using RMDQ 0-23) at four months compared to baseline, and who were prescribed two or more neuropathic pain medications, were considered to have refractory neuropathic pain. Patients with leg pain intensity levels less than 5 at four months or at least 30% reduction in leg and back pain-related disability were considered to have improved.

9.3.4 Baseline characteristics and consultations in primary care

This section provides a summary of the characteristics of patients used in the analyses in this chapter (see Table 9.2). The reader is referred to Chapter 4, section 4.9 (page 120) for a full description of the method of data collection for each characteristic.

Table 9.2 Summary of key characteristics used to describe patients with neuropathic pain medication in research in Chapter nine

Baseline characteristics	**Categorical scale**	**Continuous scale**
Sociodemographic characteristics		
Female sex	Yes/no	-
Age	-	Years
Socio-economic status	Higher managerial, administrative and professional occupations	-

Baseline characteristics	Categorical scale	Continuous scale
	Intermediate occupations	-
	Routine and manual occupations, never worked and long-term unemployed	-
Health Status		
Co-morbidities*	No other health problems	-
	One other health problem	-
	Two or more other health problems	-
	Self-reported diabetes	-
Self-reported general health	Excellent/ very good	-
	Good	-
	Fair	-
	Poor	-
Pain characteristics		
Leg pain intensity	-	0-10
Back pain intensity	-	0-10
Pain below the knee	Yes/no	-
Leg pain worse than back pain	Yes/no	-
Duration of back pain symptoms in current episode	< 6 weeks	-
	6 to 12 weeks	-

Baseline characteristics	Categorical scale	Continuous scale
	> 3 months	-
Duration of leg pain symptoms in current episode	< 6 weeks	-
	6 to 12 weeks	-
	> 3 months	-
Widespread pain[†]	Yes/no	-
Limitations in activities		
RMDQ	-	0-23
Psychological variables		
HADS (depression)	-	0-21
HADS (anxiety)	-	0-21
PSEQ[‡]	-	0-60
Neurological examination findings		
Presence of muscle weakness[§]	5/5	-
	4/5	-
	0 to 3/5	-
Presence of either reduced or absent lower limb reflex	None	-
	Slightly reduced	-
	Significantly reduced or absent	-
Reduction or loss of sensation to pin-prick	Yes/no	-

Baseline characteristics	Categorical scale	Continuous scale
Presence of pins and needles	Yes/no	-
Presence of allodynia or hyperalgesia in the leg(s) [‖]	Yes/no	-
Neural tension test[**] (any positive test)	Yes/no	-
Other Neuropathic pain definitions		
Clinical diagnosis of sciatica[††]	Yes/no	-
Persistent neuropathic pain at four months	Yes/no	-
Neuroimaging		
Evidence of nerve root compression on MRI	Yes/no	-
Primary care consultations		
Consultations with a GP or specialist nurse practitioner[‡‡]	1 to 3 visits	-
	4 to 6 visits	-
	More than 7	-

Abbreviations: HADS, Hospital Anxiety and Depression scale. GP, general practitioner, MRI, magnetic resonance imaging. PSEQ, pain self-efficacy questionnaire. RMDQ, Roland Morris Disability Questionnaire (RMDQ) leg version

* Co-morbidities include self-reported history of chest problems, heart problems, raised blood pressure, diabetes and circulation problems in the leg

[†] Widespread pain was defined as pain present above and below the waist, in the right- and left-hand sides of the body and in the axial skeleton

[‡] Higher scores on PSEQ reflect stronger self-efficacy beliefs

[§] Muscle strength was tested according to a 6-point grading scale where;

0. No visible flicker of movement or contraction
1. Flicker of movement
2. Full active movement with gravity counterbalanced
3. Full active movement against gravity but not applied resistance
4. Full active movement against gravity and some applied resistance
5. Full active movement against gravity and strong resistance

|| Hyperalgesia is an increased pain response to painful stimuli. Allodynia is pain response to non-painful stimuli (for example, brush strokes)
** Neural tension tests; straight leg raise, femoral stretch and slump test
†† LBLP patients with a clinical diagnosis of sciatica are described as having "possible" neuropathic pain ((Treede et al. 2008, Finnerup et al. 2016)
‡‡Number of consultations for the four month period before the date of index consultation at the ATLAS research clinic, and for the four month period thereafter. Data for consultations was derived from electronic medical records.

9.4 Statistical analysis

9.4.1 Patterns of pain medication prescriptions

The frequency (percentage) of pain medication prescriptions within the electronic records of individual patients was summarised for LBLP patients with neuropathic pain (based on three definitions of neuropathic pain) four months before and after index consultation at the ATLAS research clinic. The frequency of one or more of the six categories of medications (first line neuropathic pain medication, basic pain medication, weak or moderate opioids, strong or very strong opioids, non-steroidal anti-inflammatory medication and skeletal muscle relaxants) and individual medications within these categories that were prescribed up to four months after index consultation at the ATLAS research clinic were summarised for patients with neuropathic pain. Next, the number of pain medication prescriptions for patients up to twelve months and then up to three years after index consultation at the ATLAS research clinic were estimated.

9.4.2 Baseline characteristics and consultations in primary care

Descriptive statistics (mean and SD for continuous variables and frequency and percentage for categorical variables) were used to describe characteristics of LBLP patients with neuropathic pain and the number of primary care consultations for those

patients prescribed neuropathic pain medication up to four months after index consultation at the ATLAS research clinic and to compare these patients with those not prescribed such medications.

9.4.3 Estimates of LBLP patients with refractory neuropathic pain

The proportion of LBLP patients with neuropathic pain (based on three definitions of neuropathic pain and one definition of persistent neuropathic pain) with a clinically important difference in terms of leg pain intensity or leg and back pain-related disability was estimated and then described for those patients who were prescribed one or more neuropathic pain medications up to four months after index consultation at the ATLAS research clinic compared to those who are not. The proportion of LBLP patients with refractory neuropathic pain was reported.

The analyses presented in this chapter uses data from patients who completed questionnaires at baseline and at four months. As documented in previous chapters there was some uncertainty due to missing data at follow-up. Sensitivity analyses were carried out comparing analyses using complete cases and those using imputed data (the reader is referred to Chapter 4, section 11; Study design and methods, for full details of the development of the imputation model and the assumptions made), a comparison of the two analyses was carried out which is summarised in section 9.5.3 and the results of these analyses are presented in the Appendix C.

9.5 Results

The pain medications prescribed to patients with neuropathic pain are summarised in section 9.5.1 (Tables 9.3 and 9.4). A description of the baseline characteristics and the number of primary care consultations for those patients who were prescribed neuropathic pain medications by four months compared to those who were not is given in section 9.5.2 and in Table 9.5. The penultimate section (section 9.5.3) summarises the change in pain intensity or LBLP-related disability in those patients who were prescribed neuropathic pain medications compared to those who were not, this is also depicted in Figure 9.1. Finally, section 9.5.4 highlights an estimated proportion of patients with refractory neuropathic pain in this patient population.

9.5.1 Patterns of pain medication prescriptions

9.5.1.1 Comparing patients with neuropathic pain across three definitions

Over eight out of ten (81.7%) of patients with neuropathic pain based on s-LANSS were prescribed at least one pain medication up to four months before and after index consultation at the ATLAS research clinic, the majority (164 out of 273, 60.1%) of patients were prescribed two or more pain medications. The proportion of patients prescribed pain medications was similar across all three definitions of neuropathic pain, this was consistent across all six groups of pain medications and similar for all individual medications within each category. Table 9.3 summarises the number of individual pain medications that were prescribed for LBLP patients based on three definitions of neuropathic pain four months before and after index consultation at the

ATLAS research clinic and is followed by a detailed report of the pain medications prescribed to patients with neuropathic pain based on one definition (s-LANSS).

The category of medications most commonly prescribed were weak or moderate strength opioids, nearly six out of ten patients with neuropathic pain (n=159, 58.2%) received a prescription for these types of drugs. Approximately a third of patients were prescribed basic analgesics (n=95, 34.8%) and similarly a third of patients were prescribed non-steroidal anti-inflammatories (n=91, 33.3%). Just under three out of ten patients (n=80, 29.3%) were prescribed one or more first line neuropathic pain medications and over a quarter (n=71, 26.0%) were prescribed either strong or very strong opioids. Skeletal muscle relaxants (Diazepam) was the least common category of medication to be prescribed, for approximately one in ten patients (n=31, 11.4%).

Co-codamol was the most commonly prescribed individual medication to these patients, over half (of those with neuropathic pain based on s-LANSS n=144, 52.8%) were prescribed Co-codamol up to four months before and after index consultation at the ATLAS research clinic, Naproxen was prescribed for over a quarter of patients (n=70, 25.6%), followed by Amitriptyline (n=66, 24.2%) and Tramadol to one in five patients (n=56, 20.5%). Over a quarter of patients were prescribed one neuropathic pain medication (including Tramadol) (n=72, 26.4%) and one in ten patients were prescribed two or more (n=33, 11.3%). Amitriptyline was the most frequent first line neuropathic pain medication prescribed, followed by Gabapentin (n=17, 6.2%). Pregabalin was prescribed for very few patients (n=7, 2.6%) and Duloxetine was rarely prescribed (n=1 0.4%). A small proportion of patients (n=24, 8.8%) were prescribed

Amitriptyline and Tramadol four months before or after an index consultation in primary care.

*Table 9.3 Pain medication prescribed in primary care for patients with neuropathic pain up to four months before and after index consultation**

	Neuropathic pain definition		
Number of pain medications prescribed for individual patients	*s-LANSS≥ 12 (n=273)*	*Clinical diagnosis of sciatica (n=423)*	*Clinical diagnosis of sciatica with clear or possible nerve root compression on MRI (n=232)*
Total pain medications			
None	50 (18.3)	83 (19.6)	44 (19.0)
One	59 (21.6)	105 (24.8)	47 (20.3)
Two or more	164 (60.1)	235 (55.6)	141 (60.8)
Basic pain medications (one or more)	**95 (34.8)**	**125 (29.6)**	**72 (31.0)**
Paracetamol	51 (18.7)	70 (16.6)	37 (16.0)
Ibuprofen (200mg-400mg)	42 (45.4)	51 (12.1)	30 (12.9)
Topical NSAIDs	21 (7.7)	28 (6.6)	18 (3.5)
First line neuropathic pain medication (one or more)	**80 (29.3)**	**117 (27.7)**	**75 (32.3)**
Amitriptyline	66 (24.2)	101 (23.9)	62 (26.7)
Gabapentin	17 (6.2)	24 (5.7)	18 (7.8)
Duloxetine	1 (0.4)	1 (0.2)	1 (0.4)
Pregabalin	7 (2.6)	7 (1.7)	5 (2.2)

	Neuropathic pain definition		
Number of pain medications prescribed for individual patients	*s-LANSS≥ 12 (n=273)*	*Clinical diagnosis of sciatica (n=423)*	*Clinical diagnosis of sciatica with clear or possible nerve root compression on MRI (n=232)*
Weak to moderate opioids (+/- combination with paracetamol) (one or more)	**159 (58.2)**	**252 (59.6)**	**144 (62.1)**
Co-codamol	144 (52.8)	223 (52.7)	130 (56.0)
Codeine (≤15mg)	7 (2.6)	13 (3.1)	6 (2.6)
Nefopam†	10 (3.7)	16 (3.8)	7 (3.0)
Co-dydramol	9 (3.3)	14 (3.3)	11 (4.7)
Others	2 (0.7)	2 (0.5)	2 (0.9)
Strong to very strong opioids (one or more)	**71 (26.0)**	**104 (24.6)**	**64 (27.6)**
Tramadol (≥50mg)	56 (20.5)	90 (21.3)	56 (24.1)
Dihydrocodeine (≥30mg)	21 (7.7)	27 (6.4)	13 (5.6)
Codeine (≥30mg)	15 (5.5)	14 (3.3)	8 (3.5)
Others	8 (2.9)	10 (2.4)	9 (3.9)
NSAIDS (one or more)	**91 (33.3)**	**136 (32.2)**	**87 (37.5)**
Naproxen	70 (25.6)	114 (27.0)	71 (30.6)
Others	28 (10.3)	37 (8.8)	29 (12.6)

	Neuropathic pain definition		
Number of pain medications prescribed for individual patients	*s-LANSS≥ 12 (n=273)*	*Clinical diagnosis of sciatica (n=423)*	*Clinical diagnosis of sciatica with clear or possible nerve root compression on MRI (n=232)*
Skeletal muscle relaxants (Diazepam)	**31 (11.4)**	**49 (11.6)**	**37 (16.0)**

All figures are frequencies (percentage) of prescriptions to an individual
* Prescribing data was obtained for the four month period before the date of first attendance at the ATLAS study research clinic and four month thereafter
†Nefopam acts through central mechanisms distinct to the action of opioids but is considered to be equipotent with opioids of moderate strength

The following section (9.5.1.2) reports the pain medications prescribed to LBLP patients with neuropathic pain up to three years after index consultation at the ATLAS research clinic. Section 9.5.2 then describes the baseline characteristics of patients with neuropathic pain based on one definition of neuropathic pain (s-LANSS) who were prescribed one or more neuropathic pain medications compared to those who were not.

9.5.1.2 Comparing prescribing patterns of pain medication across three different time points

The majority of prescriptions for pain medication were issued at or before the first four months following index consultation at the ATLAS research clinic. By three-years, three-quarters of patients (n=207, 75.8%) had been prescribed two or more pain medications, few patients (n=34, 12.5%) were not prescribed any pain medication, this is summarised in Table 9.4.

Table 9.4 Pain medication prescribed in primary care for patients with neuropathic pain (based on s-LANSS) up to four months before and three years after index consultation

Number of pain medications prescribed for individual patients	Follow-up (n=273) *		
	Four months	*Twelve months*	*Three years*
None	50 (18.3)	43 (15.8)	34 (12.5)
One	59 (21.6)	45 (16.5)	32 (11.7)
Two or more	164 (60.1)	185 (67.8)	207 (75.8)

All figures are frequencies (percentages) and figures at twelve months and three years are cumulative
* Prescribing data were obtained for the four month period before the date of index consultation at the ATLAS research clinic and four, twelve months and three years thereafter.

9.5.2 Baseline characteristics of patients with neuropathic pain prescribed neuropathic pain medication

Nearly four out of ten (n=105, 38.5%) LBLP patients with neuropathic pain based on s-LANSS were prescribed one or more of the five pain medications recommended for treatment of neuropathic pain (Amitriptyline, Duloxetine, Gabapentin, Pregablin or Tramadol) up to four months before and after an index consultation the ATLAS research clinic. The baseline characteristics of patients who were issued with at least one of the neuropathic pain medications (including Tramadol) compared to those who were not are summarised in Table 9.5. The mean age of these patients was older (52.2 (SD 13.3) years) compared to those who were not prescribed these medications (48.6 (13.4) years). A higher proportion of patients were in routine or manual occupations, had never previously worked or were unemployed were prescribed one or more neuropathic pain medications (67 out of 105, 69.1%) compared those who were not

(86 out of 168, 51.5%). Mean leg pain intensity (using NRS 0 to 10) reported by patients prescribed these medications was higher (6.6 (2.2)) compared to those who were not (5.3 (2.2)). They also more frequently reported leg pain that was worse than back pain (59 out of 105, 56.2%, vs 71 out of 166, 42.8%) and the presence of pins and needles (82 out of 105, 78.1% vs 112 out of 168, 66.7%). Mean LBLP-related disability (using RMDQ 0 to 23) was higher at baseline in patients prescribed neuropathic pain medication (15.5 (5.2)) compared to those who were not (12.8 (5.6)). They also had higher mean scores for depression symptoms (using HADS 0 to 21, 8.6 (4.1) vs 6.5 (4.2)) and lower mean pain self-efficacy (using PSEQ 0 to 60, 26.4 (15.3) vs (33.4 (13.8)) than those patients who were not prescribed these medications. More patients prescribed medications recommended for neuropathic pain had evidence of nerve root compression on MRI (58 out of 93, 62.4%) compared to those without such prescriptions (73 out of 156, 46.8%). Patients who consulted with GP on more than seven occasions four months before and after an index consultation at the ATLAS research clinic were more frequently prescribed neuropathic pain medication (67 out of 105, 63.8% compared to 60 out of 168, 35.7%).

*Table 9.5 Baseline characteristics of LBLP patients with neuropathic pain (based on s-LANSS) by neuropathic pain medication prescribed four months before and after index consultation**

		Neuropathic pain medication prescription†	
Baseline characteristics (n=273)		*None* *N=168 (61.5%)*	*One or more* *N=105 (38.5%)*
Sociodemographic characteristics			
Female		111 (66.1)	72 (68.6)
Age (years), mean (SD)		48.6 (13.4)	52.2 (13.3)
Socio-economic status (n=264)	Higher managerial, administrative and professional occupations	38 (22.8)	8 (8.3)
	Intermediate occupations	43 (25.8)	22 (22.7)
	Routine and manual occupations, never worked and long-term unemployed	86 (51.5)	67 (69.1)
Health Status			
Co-morbidities‡	No other health problems	108 (64.3)	60 (57.1)
	One other health problem	35 (20.8)	33 (31.4)

Baseline characteristics (n=273)		Neuropathic pain medication prescription†	
		None *N=168 (61.5%)*	*One or more* *N=105 (38.5%)*
	Two or more other health problems	25 (14.9)	12 (11.4)
	Self-reported diabetes	14 (8.3)	11 (10.5)
Self-reported general health (n=272)	Excellent/ very good	35 (20.8)	13 (12.5)
	Good	54 (32.1)	37 (35.6)
	Fair	71 (42.3)	35 (33.7)
	Poor	8 (4.8)	19 (18.3)
Pain characteristics			
Leg pain intensity (0-10), mean (SD) (n=261)		5.3 (2.2)	6.6 (2.2)
Back pain intensity (0-10), mean (SD) (n=271)		5.2 (1.7)	5.9 (1.3)
Pain below the knee		129 (76.8)	81 (77.1)
Leg pain worse than back pain (n=271)		71 (42.8)	59 (56.2)
Duration of back pain symptoms in current episode (n=277)	< 6 weeks	64 (38.3)	28 (26.9)
	6 to 12 weeks	34 (20.4)	25 (24.0)
	> 3 months	69 (41.3)	51 (49.0)
Duration of leg pain symptoms in current episode (n=263)	< 6 weeks	71 (44.1)	35 (35.0)
	6 to 12 weeks	33 (20.5)	20 (20.0)
	> 3 months	57 (35.4)	45 (45.0)

Baseline characteristics (n=273)		Neuropathic pain medication prescription†	
		None *N=168 (61.5%)*	*One or more* *N=105 (38.5%)*
Widespread pain § (n=269)		76 (45.5)	38 (37.3)
Limitations in activities			
RMDQ (0-23), mean (SD)		12.8 (5.6)	15.5 (5.2)
Psychological variables			
HADS (depression) (0-21), mean (SD)		6.5 (4.2)	8.6 (4.1)
HADS (anxiety) (0-21), mean (SD) (n=271)		8.4 (4.4)	9.6 (4.3)
PSEQ‖ (0-60), mean (SD) (n=266)		33.4 (13.8)	26.4 (15.3)
Neurological examination findings			
Presence of muscle weakness**	5/5	137 (81.6)	78 (74.3)
	4/5	29 (17.3)	24 (22.9)
	0 to 3/5	2 (1.2)	3 (2.9)
Presence of either reduced or absent lower limb reflex	None	139 (82.7)	68 (64.8)
	Slightly reduced	6 (3.6)	13 (12.4)
	Significantly reduced or absent	23 (13.7)	24 (22.9)
Reduction or loss of sensation to pin-prick		78 (46.4)	55 (52.4)
Presence of pins and needles		112 (66.7)	82 (78.1)
Presence of allodynia or hyperalgesia in the leg(s) ††		24 (14.3)	16 (15.2)

Baseline characteristics (n=273)		Neuropathic pain medication prescription† None N=168 (61.5%)	Neuropathic pain medication prescription† One or more N=105 (38.5%)
Neural tension test‡‡ (any positive test)		98 (58.3)	60 (57.1)
Other Neuropathic pain definitions			
Clinical diagnosis of sciatica§§		129 (76.8)	86 (81.9)
Persistent neuropathic pain at four months (n=156)		37 (39.0)	32 (52.5)
Neuroimaging			
Evidence of nerve root compression on MRI (n=249)		73 (46.8)	58 (62.4)
Primary care consultations			
Consultations with a GP or specialist nurse practitioner	1 to 3 visits	58 (34.5)	18 (17.1)
	4 to 6 visits	50 (29.8)	20 (19.1)
	More than 7	60 (35.7)	67 (63.8)

Figures are frequencies (percentages) unless stated otherwise as mean (SD) and the denominator varies for some participants due to missing data or not applicable case.
Abbreviations: HADS, Hospital Anxiety and Depression scale. IPQ-R, Illness perceptions questionnaire-revised. PSEQ, pain self-efficacy questionnaire. RMDQ, Roland Morris Disability Questionnaire leg version. SD, standard deviation. S-LANSS, self-report version of Leeds Assessment for Neurological Symptoms and Signs neuropathic pain scale.
* Prescribing data were obtained for the four month period before the date of index consultation at the ATLAS research clinic and four, twelve months and three years thereafter.
† Neuropathic pain medications: Amitriptyline, Duloxetine, Gabapentin, Pregabalin and Tramadol
‡ Co-morbidities include self-reported history of chest problems, heart problems, raised blood pressure, diabetes, and circulation problems in the leg.
§ Widespread pain was defined as pain present above and below the waist, in the right- and left-hand sides of the body and in the axial skeleton.
|| Higher scores on PSEQ reflect stronger self-efficacy beliefs
** Muscle strength was tested according to a 6-point grading scale where;
0. No visible flicker of movement or contraction
1. Flicker of movement
2. Full active movement with gravity counterbalanced
3. Full active movement against gravity but not applied resistance
4. Full active movement against gravity and some applied resistance
5. Full active movement against gravity and strong resistance.

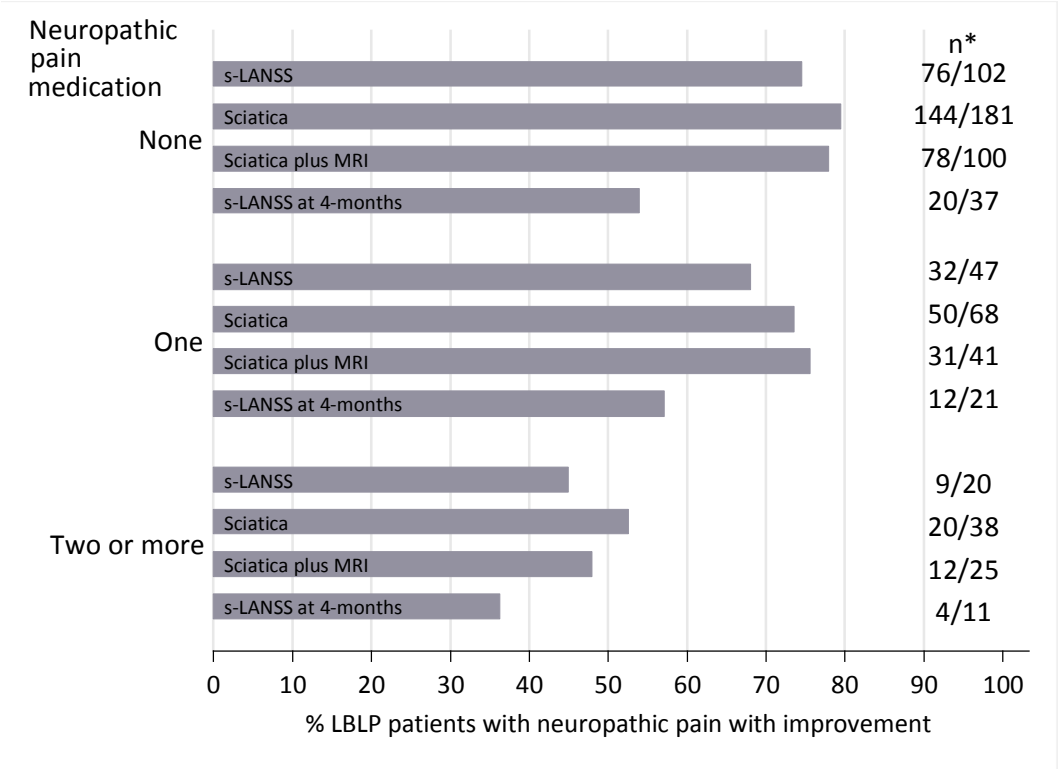
†† Hyperalgesia is an increased pain response to painful stimuli. Allodynia is pain response to non-painful stimuli (for example, brush strokes).
‡‡ Neural tension tests; straight leg raise, femoral stretch and slump test.
§§ LBLP patients with a clinical diagnosis of sciatica are described as having "possible" neuropathic pain

9.5.3 Prescribed medications and proportion of patients with neuropathic pain with improvement four months after index consultation at ATLAS research clinic

Across the three definitions of neuropathic pain, the proportion of patients who improved in terms of leg pain intensity or LBLP-related disability by four months was highest in patients with a clinical diagnosis of sciatica (214 out of 287, 74.6%). This was similar for patients with a clinical diagnosis of sciatica with evidence of nerve root compression (121 out of 166, 72.9%) and slightly lower for patients with neuropathic pain based on s-LANSS at baseline (117 out of 169, 69.2%). Just over half (36 out of 69, 52.2%) of those with persistent neuropathic pain improved in terms of leg pain intensity and leg or back pain-related disability. Figure 9.1 summarises the proportion of patients who improved four months after an index consultation at the ATLAS research clinic, based on three definitions of neuropathic pain including those with persistent neuropathic pain (s-LANSS at four months). The findings are reported in three categories summarising the neuropathic pain medication prescribed to patients up to four months before and after an index consultation at the clinic. Three-quarters (76 out of 102, 74.5%) of patients with neuropathic pain based on s-LANSS not prescribed any neuropathic pain medication improved, compared to 68% (32 out of 47) of those who were prescribed one of this group of medication and 45% (9 out of 20) who were prescribed two medications in this group. The proportion of patients with neuropathic pain based on a clinical diagnosis of sciatica (either with or without

evidence of nerve root compression on MRI) who improved was slightly higher for all three categories reporting on prescriptions for neuropathic pain medications (see Figure 9.1). Just over a half (20 out of 37, 54.1%) of patients with persistent neuropathic pain not prescribed any neuropathic pain medication improved, compared to 57.1% (12 out of 21) of those who were prescribed one of this group of medication and a third (4 out of 11, 36.4%) who were prescribed two medications in this group.

Figure 9.1 Bar chart showing proportion of patients with a clinically important difference in leg pain intensity and/or leg and back pain-related disability by four months



* Proportion (n) of patients with improvement by neuropathic pain definition in those who were prescribed one or more neuropathic pain medications compared to those who were not.

9.5.3.1 Comparison of complete case analysis versus imputed data

A sensitivity analysis was carried out using estimates from the combined results of 60 multiply-imputed datasets. The proportion of patients who improved based on complete case analysis was higher compared to those estimates based on imputed data for those patients prescribed either none, or one neuropathic pain medication (for all three definitions of neuropathic pain and those with persistent neuropathic pain based on s-LANSS). For the category of patients prescribed two or more neuropathic pain medications, estimates derived from complete case analysis and those based on imputed data were similar. See Table 9.6 for a comparison between the two types of data for one definition of neuropathic pain (s-LANSS). The reader is referred to the Appendix C for the analysis in this chapter repeated using multiply imputes data.

Table 9.6 Proportion of patients with neuropathic pain (based on s-LANSS) who improved by the number of neuropathic pain medications prescribed, comparing imputed data and data using complete cases

	Estimates derived from complete case analysis		**Estimates derived from multiple imputation**	
Number of neuropathic pain medications*	*N*	*Proportion (%)*	*Proportion (%)*	*95% Confidence Interval†*
None	76	74.5	68.3	60.5 to 76.0
One	32	68.1	60.6	47.6 to 73.7
Two or more	9	45.0	50.8	31.0 to 70.6

* Neuropathic pain medications: Amitriptyline, Duloxetine, Gabapentin, Pregabalin and Tramadol
† Confidence intervals are for certainty around a point estimate for imputed data

9.5.5 Estimates of LBLP patients with refractory neuropathic pain

Seven patients with neuropathic pain at baseline and at four months (those defined as having persistent neuropathic pain) reported leg pain intensity greater than 5 or less than 30% reduction in leg and back pain-related disability despite having been prescribed two or more different neuropathic pain medications. These patients were considered to have refractory neuropathic pain. A sensitivity analysis was completed using a second definition of persistent neuropathic pain, based on a clinical diagnosis of sciatica at baseline and the presence of pain below the knee at four months. Results showed that the number of patients with refractory neuropathic pain was two (out of 111).

The following section discusses the prescribing patterns of pain medications in LBLP patients with neuropathic pain and the challenges of estimating the scale of the problem of refractory neuropathic pain in this patient population.

9.6 Discussion

The aims of research within this chapter were to estimate and describe prescribing patterns of pain medications in LBLP patients with neuropathic pain who consult in primary care and to provide estimates of LBLP patients with refractory neuropathic pain. In this section the results are discussed and compared to previous literature. As in previous chapters, the strengths and weaknesses of these analyses are discussed

before considering the implications of the results for clinical practice and future research.

9.6.1 Prescribing patterns of pain medications in LBLP patients with neuropathic pain

This research described the pain medication prescribed for patients with neuropathic pain four months before and after an index consultation in the ATLAS research clinic, this is believed to be novel research in this group of patients with LBLP. The results showed that in the defined time period over 80% of LBLP patients with neuropathic pain were prescribed at least one pain medication in primary care. This was consistent using two definitions of "possible" neuropathic pain and one of "probable" neuropathic pain. This is comparable to previous research reporting a similar proportion (83%) of patients with neuropathic pain who were prescribed pain medication in primary care (Berger et al. 2012). Describing the current prescription practice of pain medication in this patient population is important, as both patients and clinicians rely on pain medication for adequate management and relief of neuropathic pain symptoms (Smith et al. 2012b, Closs et al. 2007), and such prescription data can lead to an improved understanding of the prescribing practice in primary care for LBLP patients with neuropathic pain.

Up to one third of patients with neuropathic pain were prescribed one or more first line neuropathic pain medications (Amitriptyline, Gabapentin, Pregablin and Duloxetine), which is a similar proportion and is comparable to previous studies investigating neuropathic pain medication use in neuropathic LBP and neck pain

conditions (Gore et al. 2007). In this research, Amitriptyline was the most frequently prescribed first line neuropathic pain medication, prescribed to approximately one quarter of patients (24% of patients with neuropathic pain based on s-LANSS) in the period before and after an initial consultation in primary care. Amitriptyline is recommended as the first choice neuropathic pain medication in primary care for patients with neuropathic pain conditions (Smith et al. 2012b) and previous research based in UK primary care settings report a similar proportion of patients with neuropathic LBP prescribed Amitriptyline (22%) (Hall et al. 2013). The majority of patients are not treated with neuropathic pain medication and previous cross-sectional research (Gore et al. 2007, Torrance et al. 2013) has suggested that this points towards sub-optimal prescribing of medication for neuropathic pain. A discussion follows in section 9.6.3 (page 337) highlights whether the findings of this research suggest more patients in this population should be prescribed neuropathic pain medications.

In this research weak to moderate strength opioids were the most commonly prescribed group of medications, approximately 60% of patients were prescribed medication of this type during the study period (four months up to and after the research clinic visit). Nearly as many as seven out of ten patients (69%) with neuropathic pain were issued a prescription for an opioid of any strength in the same study period. By comparison, this estimate appears to be over twice as high as previous estimates, for example the UK study by Ashworth et al. (2013) reported 33% of LBP patients with and without leg pain were prescribed opioids within a period of 14

days before and 28 days after consultation for LBP without or without leg pain, in primary care. When the sampling period in the current research was adjusted to be the same as in the study by Ashworth et al. (2013), 47% of patients had evidence in their record of a prescription for an opioid drug. It seems that more patients in the ATLAS cohort were prescribed opioid pain medication than the broader group of patients with LBP consulting in primary care. Higher prescribing may be appropriate given that LBLP patients with or without neuropathic pain consult in primary care with worse pain and back-pain related outcomes compared to those with LBP alone (Hill et al. 2011a, Konstantinou and Dunn 2008). There is limited evidence for the effectiveness of opioids in LBP pain conditions with or without neuropathic pain (Dowell et al. 2016) and opioids are now the most commonly prescribed type of medication in the United States (US) (Ivanova et al. 2011) which is currently thought of as an epidemic associated with at worst, dependency and death due to overdose (McCarthy 2012). It was beyond the scope of the research in this thesis to investigate whether LBLP patients with neuropathic pain responded to opioid medication, but may be the focus of future research given the high proportion of prescriptions to patients with neuropathic pain.

Tramadol in this research is defined as a specific neuropathic pain medication (NICE CG173 2013) and can be considered in addition to other medications for patients with neuropathic pain (Smith et al. 2012b). Tramadol acts as both an opioid and a serotonin reuptake inhibitor (examples of other serotonin reuptake inhibitors are Citalopram and Sertraline which are used as anti-depressants) and a norepinephrine reuptake

inhibitor, it is suggested to be an effective type of pain medication for nociceptive pain and may be effective for neuropathic pain conditions (Duehmke et al. 2017). The proportion of patients prescribed Tramadol was lower in this research (21%) of LBLP patients than in previous research (Hall et al. 2013) of patients with neuropathic LBP (34%). LBP and LBLP are mixed pain conditions but LBLP is more often neuropathic than LBP (the reader is referred to Chapter 1 (section 1.5) for details of the distinction between LBP and LBLP in terms of pain mechanisms). It is likely that the sample of patients in the study by (Hall et al. 2013), unlike the current study, was not exclusively a cohort of LBLP patients and perhaps were prescribed Tramadol for nociceptive pain. The following section (9.6.2) discusses some of the key characteristics of patients who were prescribed neuropathic pain medication (including Tramadol) in the current study compared to those who were not.

9.6.2 Characteristics of patients prescribed neuropathic pain medication

It is apparent that patients prescribed at least one neuropathic pain medication (including Tramadol) had more severe leg pain intensity, higher LBLP-related disability and lower pain self-efficacy than those patients not prescribed such medication. This seems appropriate and in line with guidelines as pain severity and its impact on lifestyle including daily activities are key indications for treating patients with neuropathic pain with specific pain medication (NICE CG173 2013). Over two thirds (64%) of patients with neuropathic pain prescribed a neuropathic pain medication consulted with their GP on at least seven occasions four months preceding the index consultation at the research study clinic and up to four months after. This estimate

was higher than expected, as the crude annual consultation rate for persons attending primary care in the UK is 5 per person-year (Hobbs et al. 2016) but it is not clear whether patients consulted a lot before they were prescribed the medication, or whether they consulted more as a consequence of having a prescription for medication, for example for clinical reviews, or whether they consulted more despite having a prescription for neuropathic pain medication. In the ATLAS cohort, there was no evidence to suggest that patients who were issued with neuropathic pain medication reported more co-morbidities, poorer self-reported general health or more widespread pain at baseline compared to those who were not prescribed these medications. This suggests that patients who were prescribed neuropathic pain medications consulted predominantly for pain-related reasons such as clinical reviews to assess treatment effectiveness (NICE CG173 2013) or that these patients were not receiving adequate pain relief and re-consulted to seek further treatment.

Patients who were prescribed one or more neuropathic pain medications more often reported leg pain worse than back pain, and pins and needles in the painful leg. During brief consultations in primary care, it is plausible that non-specialist clinicians such as GPs, identify patients with neuropathic pain by signs and symptoms such as leg pain worse than back pain and, or presence of pins and needles. This is not an unreasonable approach as the presence of pins and needles has been identified as a potential indicator of neuropathic pain (Smith et al. 2012a) and leg pain is more likely to be neuropathic than back pain alone. However, in the research reported in this thesis, neither of these characteristics were consistently associated with neuropathic pain

across all the three definitions of neuropathic pain in LBLP patients at baseline (see Chapter 5, Table 5.5 for a summary of characteristics that were consistent across three definitions of neuropathic pain) nor was there any evidence that any of these characteristics were associated with persistent neuropathic pain at four months follow-up (see Chapter 8, section 8.5.3 Exploratory prognostic factor research, for a detailed report of potential prognostic factors associated with persistent neuropathic pain at four months).

In this study, most patients had an MRI for research purposes, but this does not reflect normal clinical practice in primary care and patients with neuropathic pain (based on s-LANSS) who were prescribed neuropathic pain medication more often were found to have evidence of nerve root compression on MRI compared to those without. Whilst the MRI results were not available at the patients' initial assessment in the ATLAS clinic, eventually the results were communicated back to the patient's GP at some point during the patient's treatment or, at the point of discharge from physiotherapy treatment in the ATLAS study. Whilst it appears that patients with evidence of nerve root compression on MRI were more likely to be prescribed pain medications, those patients with a clinical diagnosis of sciatica and evidence of nerve root compression on MRI were issued with a similar proportion of pain medications compared to the other neuropathic pain definitions.

Patients prescribed specific neuropathic pain medication tended to be older and in routine, manual occupations, had never worked or were unemployed compared to those who were not. There is some evidence from the published literature that

primary care clinicians prescribe medications in general more often to older than younger patients (Macfarlane et al. 2012). Pain severity and the extent that pain interferes with daily life can increase with advancing age (Thomas et al. 2004) and older patients may be more willing to try neuropathic pain medication and may be less willing to try other approaches such as exercise (Macfarlane et al. 2012).

Much of the evidence on how pain medication is prescribed in musculoskeletal pain focusses on opioid prescribing (for example qualitative research by Hutchinson et al. (2007) and Seamark et al. (2013)) as opioid use is associated with serious risks including overdose and death (Dart et al. 2015, Dowell et al. 2016). However, the prescription rates of neuropathic pain medications such as Pregabalin and Gabapentin have increased over recent years (Wettermark et al. 2014) and there are some concerns that such medications are associated with misuse including suicide (Schifano 2014). Despite guidelines advocating the use of neuropathic pain medications in patients with neuropathic pain irrespective of clinical condition (NICE CG173 2013) and more specifically in patients with sciatica (NICE NG59 2016), little is known about what factors influence clinicians to prescribe these medications to LBLP patients. Future research may help to understand characteristics that predict which LBLP patients benefit from neuropathic pain medication.

9.6.3 Refractory neuropathic pain

The majority (approximately seven out of ten) of LBLP patients with neuropathic pain irrespective of neuropathic pain definition, improved in terms of a clinically important difference in leg pain intensity or LBLP related disability by four months follow-up and

therefore did not have refractory neuropathic pain. Whilst the design of this research does not permit robust comparison of treatment effectiveness of these medications, the findings suggest patients with neuropathic pain improve without specific neuropathic medications and that patients who are prescribed these drugs do not appear, on average, to have better clinical outcomes than those who are not. This research questions the call by some authors of previous research (Gore et al. 2007, Torrance et al. 2013) for greater prescribing of these medications for patients with neuropathic pain. This research also supports the notion that the majority of this patient population in primary care utilise few health care resources whilst a few utilise the most (Dunn et al. 2006, Stewart et al. 2015). A much smaller proportion of patients who were prescribed more than one neuropathic pain medication improved in terms of leg pain intensity or LBLP-related disability. It is likely that high levels of leg pain intensity or disability may have been the reasons for prescribing two or more neuropathic pain medications and suggests the presence of unmeasured confounding, the consequence being imprecision in estimates. In epidemiology this type of confounding is known as confounding by indication which is common when observational data using prescribing records (for example see Gross et al. (2009)) are examined to compare patients treated with different therapies (for example none vs one or more pain medications) (Vandenbroucke et al. 2014). Methods such as the propensity score (Haukoos and Lewis 2015) based on multivariable sample sizes are used to reduce the likelihood of confounding in observational data and require larger sample sizes than in this research. In this research the influence of potential

confounders cannot be ruled out, however there is also ongoing uncertainty regarding the effectiveness of individual neuropathic pain medications (Mathieson et al. 2017).

The current research estimates that of the LBLP patients with neuropathic pain (a total of 169 patients) only seven (4%) had refractory neuropathic pain at four months based on a definition of refractory pain. When an alternative definition for persistent neuropathic pain was used the estimated proportion of refractory neuropathic pain remained very low (2 out of 111 or 2%). This is the first research to estimate the scale of the problem of refractory neuropathic pain in LBLP patients who consult in primary care using a definition of refractory neuropathic pain for which there is some consensus (Smith et al. 2012a). A previous survey of the UK general population identified 10 individuals with chronic pain which was neuropathic and refractory in nature out of 2,202 individuals with chronic pain, or 0.5% (Torrance et al. 2013). The estimate in this research is slightly higher which is not surprising since it is based on patients consulting in primary care rather than individuals sampled from the general population who are living with, but not necessarily consulting with, chronic pain. It is important to understand the extent to which patients with neuropathic pain who consult in primary care are affected by refractory pain as these patients are likely to be the most frequent users of health care services and the most likely to be referred to specialist pain services for further intensive and more expensive treatments.

It has been estimated that over half of patients will not respond to an individual neuropathic pain medication (Moore et al. 2013). The decision in the research to define refractory pain as the use of two neuropathic pain medications rather than

three or even four medications was made on the evidence that this patient population rapidly improve in terms of pain intensity and leg and back pain-related disability within the first four months after consulting with LBLP (see Chapter 6, section 6.5.3 (page 223)). There is some agreement that patients with pain that is refractory use three or four neuropathic medications (Smith et al. 2012a) and this may have led to some classification of patients whose pain was not refractory but who may have benefited from a trial of a third medication. The absolute impact of this is likely to be very low as the number of patients with refractory neuropathic pain based on the use of two neuropathic medications was so small in this study. This is the first validation of the definition of refractory neuropathic pain proposed by Smith et al. (2012a) in this LBLP patient population in primary care which is important as LBLP patients with neuropathic pain are among the most common presentations of neuropathic pain in primary care. Comparisons of the scale of the problem of refractory neuropathic pain between primary care settings and specialist pain centres may be useful information for clinicians and pain researchers.

9.6.4 Strengths and limitations

The main strength of this research is the prospective study design using electronic prescribing and consulting records linked to patients in the ATLAS study, this allowed for a detailed description of medication use and improvement in symptoms over time and allowed for an estimation of the proportion of patients with refractory neuropathic pain. Other strengths include the large sample size and completeness of the general practice medical records (more than 94% of prescription data could be

accessed for this research). General practice medical records have accurate, complete and valid data for 99% of prescriptions and 98% of consultations (Hassey et al. 2001).

A number of limitations have been identified that may have an impact on the interpretation of the findings of the analyses in this chapter. Firstly, the categorisation of pain medications did not account for medications that were used together which is common clinical practice (Bennett 2015) or sequentially. Understanding whether medications were prescribed sequentially or in combination would give a better understanding of the prescribing patterns of clinicians in primary care but was beyond the scope of this research. Secondly, it was not possible to determine whether patients were prescribed an adequate trial of a particular medication (Smith et al. 2012a) as this was secondary analysis of existing data and this information was not recorded in the dataset. The likely effect of accounting for an adequate trial of medication would be to make the definition of refractory neuropathic pain more stringent, thus reducing the number of patients with refractory pain further. Thirdly, the duration of pain medication use prior to study participation was unknown, in part this was accounted for by collecting data on prescriptions for the four months before the index consultation in the research clinic. The implication of not knowing the duration of pain medication use is that such prescriptions may have been made for other pain conditions, with the likely effect being an over-estimation of the reported findings. Fourthly, the analysis in this chapter included Nefopam as an equipotent pain medication to opioids of weak to moderate strength, this may have led to over-estimation of the proportion of patients prescribed opioid medications. However, the

absolute number of patients who were prescribed Nefopam was small (4% (n=10) of patients with neuropathic pain based on s-LANSS) and the interpretation of the results remains the same with or without those prescribed Nefopam.

Although the information on pain medication prescription was of high quality and complete for 94% of participants, there was considerable loss to follow-up from the self-report data collection (questionnaires) at four months. The analyses in the research reported in this chapter were based on complete cases which can lead to erroneous findings, especially in categories with smaller numbers, for example the number of patients who responded to follow-up at four months and were prescribed two or more neuropathic pain medications was low (n=20, based on s-LANSS). Estimates derived from combining the results of multiply-imputed datasets were more conservative than those derived using complete case analysis for patients who were prescribed at least one neuropathic pain medication and similar for those prescribed two or more of this type of medication. This suggests that the estimate of refractory pain using complete case analysis is justified in this research.

9.6.5 Implications for clinical practice and research

Perceptions by clinicians that neuropathic pain in this patient population is in large part refractory is not borne out in this research. The implication being that patients with and without neuropathic pain medication improve over time. However, pain medication including opioid medication is commonly prescribed despite strong evidence of benefit from previous research, this evidence may inform policies and guidelines on appropriate prescribing in this patient population.

The findings from this research cannot confirm or refute whether the prescription of neuropathic pain medication reduces suffering in this patient population. However, the findings appear to question the effectiveness of these medications. Future research is needed to determine the effectiveness of neuropathic pain medications, and indeed other treatments, for this patient population. Research that seeks to better understand the prescribing patterns in primary care for this patient population both in terms of qualitative and/or observational research with clinicians and patients would also be useful. Further validation of the definition of refractory neuropathic pain used in the analyses in this chapter is also recommended, in primary care settings and also in specialist pain centres.

9.7 Conclusions

In this chapter, the pain medications prescribed for LBLP patients with neuropathic pain, and in particular specific neuropathic pain medications, were investigated and an estimate of the proportion of patients with refractory neuropathic pain was reported. It appears that the recommendations within current national guidelines for prescribing neuropathic pain medications are generally adhered to. The majority (over 80%) of patients were prescribed some pain medication up to four months before and after attending the ATLAS research clinic, a third were prescribed specific neuropathic pain medications. Those patients who were prescribed one or more neuropathic pain medications had more severe leg pain intensity and higher LBLP-related disability. Seven patients or 4% (out of 169) were identified as having refractory neuropathic pain suggesting that few patients with persistent neuropathic pain also have refractory pain

in primary care. Further research could usefully contribute to a better understanding of the effectiveness of neuropathic pain medications in this patient population.

Chapter Ten. Discussions and conclusions

The aim of this thesis was to investigate the epidemiology of neuropathic pain in LBLP patients who consult in primary care based on cases identified by clinical examination and through the use of a validated, self-completed case ascertainment tool. Figure 10.1 highlights the key findings of this thesis. Some of these findings were novel and challenge commonly held assumptions in the clinical and research field of neuropathic pain whilst some findings add further evidence to existing research in the field. This chapter provides a synthesis of the key findings in this thesis and critically evaluates the strengths and limitations of the research. The implications of this work for clinical practice are then discussed before reflecting on how the findings can inform future research.

Figure 10.1 Key findings of the thesis

Systematic review

A synthesis of published literature highlighted the gap of epidemiological research in this patient population, in particular there was a paucity of evidence from prognostic research.

- Prevalence estimates varied widely (from 5% to 80%) depending on the definition of neuropathic pain.
- There was some evidence of: i) higher levels of LBLP-related morbidity in patients with neuropathic pain compared to those without, ii) more frequent reporting of LBLP-related morbidity in patients with neuropathic pain based on clinical examination compared to those with neuropathic pain based on a case ascertainment tool.
- Evidence (from one analysis) suggested that the clinical course of patients with neuropathic pain was worse compared to those without, there was a paucity of evidence on prognosis and no evidence of prognostic factors in this patient population.

Prevalence and characteristics

Neuropathic pain was common. The characteristics of patients with neuropathic pain varied depending on the method used to define cases.

- Prevalence of neuropathic pain varied from 48% to 74% depending on definition, many patients clinically diagnosed with sciatica did not have neuropathic pain based on the case ascertainment tool, s-LANSS.
- Patients with neuropathic pain reported higher leg pain intensity, worse pain self-efficacy, a higher proportion had pain below the knee and sensory loss based on findings from routine neurological examination compared to those without, across three definitions of neuropathic pain.
- Patients with neuropathic pain based on s-LANSS presented with a distinct profile compared to those with a diagnosis of sciatica. LBLP-related morbidities such as depression, anxiety and worse general health were more common in patients with neuropathic pain based on s-LANSS.

Clinical course

The clinical course of patients with neuropathic pain improved rapidly up to four months after baseline consultation and showed very little improvement thereafter. The extent of the improvement depended on the definition used.

- The clinical course of patients with neuropathic pain based on s-LANSS was worse than those without, this was not the case for the two other definitions of neuropathic pain.

Change in the presence of neuropathic pain (based on s-LANSS)

The presence of neuropathic pain changed over time, it resolved in most patients, but remained persistent in a few.

- By four months 25% of patients in the study had neuropathic pain.
- A minority of patients (16%) had persistent neuropathic pain over three years. These patients presented with worse LBLP-related disability and higher leg pain intensity at baseline.

Prognosis of LBLP patients with neuropathic pain at baseline and four months

The clinical course of patients with persistent neuropathic pain was worse compared to those with non-persistent neuropathic pain, but it was difficult to identify at baseline which patients would have persistent neuropathic pain four months later.

- The clinical course of patients with persistent neuropathic pain, in terms of pain intensity, was worse up to three years after baseline compared to those without.
- There was some evidence that leg pain intensity may be associated with persistent neuropathic pain but this was only found using one definition of neuropathic pain.
- There was no evidence that prognostic factors from neurological examination (presence of pins and needles in the leg(s), a reduction or loss of pin-prick sensation in the painful leg and evidence of nerve root compression on MRI) were associated with persistent neuropathic pain at four months.

Prescribing patterns of pain medications

Pain medications were commonly prescribed to patients with neuropathic pain, with approximately three out of ten patients prescribed neuropathic pain medications. However, patients with neuropathic pain improved with or without specific neuropathic pain medication.

- Very few patients (n=7, 4%) were identified as having refractory neuropathic pain; findings support the conclusion that the scale of the problem of refractory neuropathic pain in this patient population is not substantial.

Shaded boxes highlight research based on epidemiological analysis of a prospective cohort of LBLP patients consulting in primary care.

10.1 Key findings

In the research in this thesis, neuropathic LBLP in patients was common and varied from 48% to 74% according to the definition of neuropathic pain used (Chapter 5).

There was evidence that many (68%) patients with neuropathic pain defined by a

diagnosis of sciatica were not identified as having neuropathic pain based on s-LANSS. Similarly, in the research reported in Chapter 3 (Systematic review) there was evidence that many patients with neuropathic pain based on sciatica were not identified as having neuropathic pain based on alternative neuropathic pain case ascertainment tools such as PainDETECT and DN4. The results of this thesis challenges the traditionally held belief that sciatica is a neuropathic pain condition (for example NICE NG59 2016).

In the research in Chapter 5, there were characteristics common to patients with neuropathic pain across all three definitions of neuropathic pain; patients with neuropathic pain consistently reported higher leg pain intensity, lower pain self-efficacy, a higher proportion reported pain below the knee and sensory deficits based on findings from routine neurological examination (Chapter 5). Similar to the findings of prevalence, the characteristics of patients with neuropathic pain varied depending on the method used to define cases. Patients with neuropathic pain based on s-LANSS were found to have a greater number of differences in LBLP-related morbidities compared to those with neuropathic pain based on a clinical diagnosis of sciatica with or without MRI evidence of nerve root compression. These findings were supported by the findings of previous studies highlighted in the systematic review in this thesis (Chapter 3). None of the previous studies aimed to describe the characteristics of LBLP patients with or without neuropathic pain and in part were limited by either small sample sizes or poorly defined comparator groups. Whilst the findings of previous studies are in the same direction as the findings of this research, it is this research that

provides the highest quality evidence to date on the characteristics of this patient population.

Clinical course in terms of pain intensity and LBLP-related disability was worse for patients with neuropathic pain based on s-LANSS compared to those without, but the course of patients with neuropathic pain with a clinical diagnosis of sciatica (with or without evidence of nerve root compression on MRI) was no worse compared to those without (Chapter 6). Approximately 70% of patients with neuropathic pain at baseline, irrespective of definition, reported a clinically meaningful improvement in either pain intensity or disability four months after consulting in primary care, with little improvement thereafter. This research shows that it is not the presence of neuropathic pain per se that is associated with poor prognosis, but specifically the presence of neuropathic pain defined using the s-LANSS.

The presence of neuropathic pain (based on s-LANSS) at baseline changed in the majority of patients over three years (Chapter 7). This challenges the belief that neuropathic pain, once present, is always persistent. The majority of the change in the presence of neuropathic pain had occurred by four months follow-up, when 25% of patients had neuropathic pain compared to 48% at baseline. Similarly, the most rapid improvement in the clinical course in terms of pain intensity and LBLP-related disability in patients with neuropathic pain, occurred by four months after baseline measurement. The course in terms of pain intensity of patients with persistent neuropathic pain at four months (presence of neuropathic pain at baseline and four months based on two definitions, sciatica and s-LANSS) was not characterised by a

rapid improvement in pain intensity and was worse up to three years after baseline compared with those with non-persistent neuropathic pain (Chapter 8). This suggests that neuropathic pain is not always persistent and the presence of neuropathic pain may change as the severity of a LBLP episode abates.

Identifying the factors which predict cases of persistent neuropathic pain could inform future research to identify which patients with neuropathic pain at baseline will have persistent neuropathic pain at four months. In the research in this thesis, there was no evidence that potential prognostic factors from the neurological examination (such as presence of pins and needles in the leg(s), reduction or loss of pin-prick sensation in the painful leg), or evidence of nerve root compression on MRI, were associated with persistent neuropathic pain at four months (Chapter 8). Items from the neurological examination deemed important for defining cases of neuropathic pain at baseline did not explain the presence of persistent neuropathic pain at four months. Factors considered clinically important for LBLP patients with or without neuropathic pain (pain duration, pain self-efficacy and pain intensity) were statistically associated with persistent neuropathic pain at four months. In a multivariable model higher leg pain intensity predicted cases of persistent neuropathic pain (based on one definition). Evidence from this thesis supports an argument that persistent neuropathic pain in LBLP patients may be explained more by prognostic factors common to the broader group of LBP and LBLP patients with and without neuropathic pain than those factors thought to be signs and symptoms of underlying pathophysiological neuropathic pain mechanisms. It follows then that it is likely that persistent neuropathic pain in this

patient population also responds to treatments recommended for the broader LBP and LBLP patient populations irrespective of neuropathic status.

The majority of patients (approximately 80%) with neuropathic pain (across the three definitions) were prescribed at least one pain medication in four months before and after an index consultation in primary care (Chapter 9). Patients with neuropathic pain (across three definitions) were no more likely to self-report having been prescribed or having purchased pain medication over-the-counter at baseline compared to those without (Chapter 5). A third of patients with neuropathic pain were prescribed medication recommended for first line treatment of neuropathic pain and there was evidence to suggest that patients improved with or without a prescription for this specific type of pain medication. This appears to be in line with recent evidence from a high quality randomised controlled trial (Mathieson et al. 2017) casting doubt about the effectiveness of neuropathic pain medications for this patient population. Current guidelines in the United States recommend non-pharmacological first-line treatment (Qaseem et al. 2017) rather than pharmacological care for LBP patients including LBLP patients with neuropathic pain. The research in this thesis suggests that LBLP patients with neuropathic pain based on a diagnosis of sciatica and in the absence of progressive or severe motor weakness may respond similarly to treatments to those without neuropathic pain. This challenges the current UK clinical guideline recommendations for low back pain and sciatica that advocate neuropathic pain medication for patients with sciatica (NICE NG59 2016) and recommend them as first-

line treatment for patients with neuropathic pain irrespective of condition (NICE CG173 2013).

Neuropathic pain is considered to be one of the most challenging pain syndromes to manage but this belief is not supported by the research in this thesis. Very few patients (4% based on s-LANSS) were identified as having refractory neuropathic pain, which is characterised by severe pain that does not respond to neuropathic pain medication (Chapter 9). This is a surprisingly low proportion of patients given the assumption that neuropathic pain is challenging to treat, patients with LBLP present with higher pain intensity, higher LBLP-related disability, and have poorer outcomes compared to patients with back pain alone. One consideration is that a proportion of LBLP patients without neuropathic pain and LBP patients with back pain alone either with or without neuropathic pain, also have severe pain that does not seem to respond to treatment. Future research may estimate the scale of refractory pain in a broader LBP population.

An issue raised by research in this thesis is whether neuropathic LBLP pain based on s-LANSS may be more indicative of the severity of symptoms of pain and related disability rather than a neuropathic phenotype. Signs and symptoms of neuropathic pain such as tingling, stabbing and electric shock-like pain are particularly distressing to patients (Ong et al. 2011) and the symptoms themselves can be difficult for patients to express (Yeung et al. 2017) and may be expressed in terms of pain severity (Gierthmühlen et al. 2017). Many of the findings in this research suggest that patients with neuropathic pain and persistent neuropathic pain based on s-LANSS (Chapters 5, 7 and 8) presented with higher symptoms of anxiety and depression and lower pain

self-efficacy. Patients in the sub-group of persistent neuropathic pain based on s-LANSS continued to report more severe symptoms of anxiety and depression (mean HADS score) beyond baseline compared to patients in other sub-groups (see Table 10.1). The suggestion from these findings is that patients with neuropathic pain based on s-LANSS, and in particular those with persistent neuropathic pain, did worse over time because symptoms were primarily maintained by central rather than peripheral pain mechanisms. Centrally maintained mechanisms can be implicated in both neuropathic and nociceptive pain states, and there is considerable overlap between them (Cohen and Mao 2014). Whilst it is not clear from this research whether the presence of neuropathic pain may simply indicate severe LBLP, there is an argument that patients with neuropathic pain based on s-LANSS may reflect pain mechanisms shared with neuropathic pain, rather than actual nerve pathology (McWilliams and Walsh 2017).

Table 10.1 Symptoms of anxiety and depression (mean HADS) for neuropathic pain sub-groups over three years

	Neuropathic pain sub-group† over three years			
	Non-neuropathic pain *(n=87, 43.7%)*	*Non-persistent neuropathic pain* *(n=56, 28.1%)*	*Longstanding Persistent neuropathic pain* *(n=32, 16.1%)*	*Developing neuropathic pain* *(n=24, 12.1%)*
HADS (depression) (0-21), mean (SD)				
Baseline*	5.2 (3.6)	5.1 (3.2)	7.5 (4.6)	6.3 (3.2)
12-months	3.1 (3.1)	3.4 (3.5)	7.1 (4.3)	4.7 (3.1)
3-years	3.1 (2.9)	3.2 (3.2)	6.5 (4.5)	5.4 (3.6)
HADS (anxiety) (0-21), mean (SD)				
Baseline*	6.3 (3.3)	7.0 (4.6)	9.1 (5.0)	7.0 (3.5)
12-months	4.5 (3.7)	4.9 (4.9)	8.6 (4.3)	5.4 (3.7)
3-years	4.4 (3.7)	4.4 (4.3)	7.9 (4.3)	6.2 (3.8)

Abbreviations: HADS, Hospital Anxiety and Depression scale. s-LANSS, self-report version of the Leeds Assessment of Neuropathic Symptoms and Signs neuropathic pain scale
*HADS was not available within ATLAS dataset at 4-months.
†Sub-groups: Non-neuropathic, s-LANSS < 12 at baseline and each follow-up point thereafter. Developing, s-LANSS < 12 at baseline and ≥ 12 at one or more follow-up points. Non-persistent, s-LANSS ≥ 12 at baseline and ≥ 12 at one (at most) of the three follow-up points. Persistent, s-LANSS ≥ 12 at baseline and ≥ 12 at two or more of the three follow-up points.

Patients with a clinical diagnosis of sciatica in this research met the criteria described in the hierarchical approach (Treede et al. (2008), updated by Finnerup et al. (2016)) as having either “possible” or “probable” neuropathic pain. There is some consensus for using s-LANSS (Smith et al. 2012a) for defining neuropathic pain cases. Patients with s-

LANSS score ≥ 12 are at best described as having “possible” neuropathic pain without having to meet criteria reported by either Treede et al. (2008) or Finnerup et al. (2016). In the absence of a gold standard definition of neuropathic pain, debate is on-going about the current hierarchical approach to defining neuropathic pain (Spahr et al. 2017, Kosek et al. 2016, Lynch et al. 2011). The usefulness of the hierarchical approach could be judged on whether the prognosis of cases with “probable” neuropathic pain is distinct from those with “possible” neuropathic pain. In the context of the findings of this research, there was no evidence to suggest that patients with “probable” neuropathic pain were worse at baseline or over time compared to those with “possible” neuropathic pain based on clinical examination. Patients with “possible” neuropathic pain based on s-LANSS were found to have poorer prognosis compared to those without. The clinical value of s-LANSS in this patient population may depend on whether the effects of treatment in patients with neuropathic pain based on s-LANSS (pharmacological or non-pharmacological) is superior to those identified as having neuropathic pain based on clinical examination.

There have been suggestions in the previous literature that s-LANSS is less able to differentiate between LBLP patients with and without neuropathic pain in comparison to other neuropathic pain case ascertainment tools, for example DN4 (Gudala et al. 2017). Case ascertainment tools, for example PainDETECT, LANSS, DN4 and s-LANSS described in Chapter 1 (section 1.3.1.2, (page 12)) that are commonly used in epidemiological pain research were developed using a reference standard based on clinical examination, often including patients with sciatica. There is an argument that

each tool either fails to identify patients with neuropathic pain and/or incorrectly identifies a proportion of patients without neuropathic pain in comparison to neuropathic pain based on clinical examination (Mathieson et al. 2015). Each of the tools share similar characteristics. Positive signs of neuropathic pain such as “prickling or tingling, pins and needles”, pain described as having an “electric shock or shooting” quality and “burning” are included in each tool but changes in appearance of the skin are only included in LANSS and s-LANSS. Based on the subtle differences of each tool, unique pain profiles are identified. In the absence of a gold standard for defining neuropathic pain cases this is a challenge for research and is not unique to s-LANSS. The implication of using different tools to identify cases of neuropathic pain is inevitably variation in prevalence estimates, characteristics, clinical course and prognostic factors between definitions; it is not clear what the implication is in terms of variation in response to treatment.

10.3 Strengths and limitations of the thesis

Specific strengths and limitations related to each objective in this thesis have been discussed within the preceding chapters. This section reflects more broadly on the strengths and limitations of this thesis as a whole.

The majority of patients with neuropathic pain are assessed and managed in primary care. A key strength of this research is the use of patient data from a primary care setting and is likely to be representative of other first point of healthcare contact settings. Consecutive patients consulting with LBLP with symptoms of any duration and pain severity were included in the current research making the results

generalisable to a broad spectrum of patients and not only to those with the worst symptoms. Studies often restrict eligibility of patients by pain severity or pain duration (see Attal et al. (2011) and Schafer et al. (2011) for examples) and results can only then be applied to patients with the most severe symptoms. Including consecutive patients also reduces the risk of selection bias at the point of recruitment when there are systematic differences in patients recruited compared to those who were not.

This is the first prospective cohort of LBLP patients with neuropathic pain consulting in primary care, the cohort design allowed for investigation of the temporal relationship between neuropathic pain at baseline and outcomes in terms of pain intensity, LBLP-related disability and the persistence of neuropathic pain. This is an important strength of this thesis and addresses the limitations of previous research of this patient population (for example, Hüllemann et al. 2017). A broad range of self-reported data and findings were collected from standardised clinical examination including those from MRI scans, this is an advantage of the prospective cohort study design. The majority of self-reported data was collected from validated scales in this population, for example the leg version of the RMDQ (Roland and Morris 1983, Patrick et al. 1995) to assess LBLP-related disability and the HADS (Zigmond and Snaith 1983) to assess symptoms of anxiety and depression. Using standardised approaches to define cases of neuropathic pain, characteristics and prognostic factors enabled comparisons between the results of the research in this thesis to previously published studies.

In the future, further data collection at follow-up from the clinical examination and MRI scan would address a limitation of this study (which had these times of data

collection only at baseline), albeit with extra cost and potentially greater loss to follow-up. The decision to use three definitions of neuropathic pain was driven by the absence of a perfect reference standard of neuropathic pain and allows for comprehensive prognostic research in this patient population.

A potential limitation is the loss to follow up, which is a type of selection bias. However, missing data were accounted for and results from the sensitivity analyses using imputed data were comparable to those using complete cases. A further limitation that is a disadvantage of prospective treatment cohort studies of patients and applies to the longitudinal analysis in Chapters 6 to 9 is confounding due to treatment. Patients in this cohort were managed clinically based on current best clinical evidence. Patients mainly received a course of physiotherapy care, and a small number of patients (n=70) were referred for other treatments (for example epidural injections or pain management) or for further assessment (including referrals to Extended Scope Physiotherapy practitioners in a dedicated back pain service, spinal surgeons and pain specialists). All patients received care from their GPs, and this could include prescriptions of pain medication. Physiotherapy treatment was similar across the groups according to all three definitions of neuropathic pain used in this thesis (see Chapter 6, section 6.5.1 (page 217) for a report of treatment received by patients). There is a possibility that a positive response to treatment, for example to epidural injections in patients with sciatica with evidence of nerve root compression on MRI, may have influenced the clinical course of these patients reported in this thesis. Chapter 9, section 9.6.3 (page 337) provides an account of potential risk of

confounding by indication whereby patients with more severe LBLP-related morbidity were prescribed neuropathic pain medication more frequently which is a limitation of observational study designs, the implication of this is discussed in more detail in the section 10.5 (Implications for future research).

Finally, a limitation that is worth consideration is whether the MRI findings or MRI reporting could have influenced treatment decisions in ATLAS. Firstly, the finding of possible or clear nerve root compression based on MRI was not associated with neuropathic LBLP based on s-LANSS (see Chapter 5, section 5.5.2.7 (page 165)) and this suggested the influence of MRI results on patient outcomes would have been similar for patients with and without neuropathic pain defined in this manner. Secondly, patients with neuropathic pain based on a clinical diagnosis of sciatica compared to those without (see Chapter 5, section 5.5.3 (page 175)) were over 3 times more likely to have either clear or possible nerve root compression on MRI however, only a small proportion of patients received interventions such as spinal injection or surgery because they reported worsening symptom severity which was clinically thought to be caused by the nerve root compression. Given the differences in pain and LBLP-related disability between patients with and without neuropathic pain (with or without evidence of nerve root compression) were often small with no obvious clinical relevance, the influence of MRI on treatment decisions, on patient outcomes and ultimately on the key findings of this thesis seems small.

10.4 Implications for clinical practice

The research in this thesis informs clinicians of the likely prognosis of LBLP patients with neuropathic pain consulting in primary care, which is important given that the provision of prognostic information can help patients better understand and self-manage their condition (Foster et al. 2018). The implications of research in this thesis have been discussed in preceding chapters, this section highlights the key information to be disseminated to clinicians treating this patient population in primary care.

Clinicians should be aware that neuropathic pain is common in LBLP but the prevalence and clinical characteristics are likely to vary depending on the methods used to define neuropathic pain in clinical practice. Clinicians should also be aware that sciatica is not always a neuropathic condition. Evidence of nerve root compression from MRI increases the certainty of neuropathic pain but does not change the prognosis of patients with sciatica and as recommended by clinical guidelines (NICE NG59 2016) patients should only be referred for imaging when serious pathology is suspected (for example cauda equina or malignancy) and when interventions such as surgery are being considered.

Approximately 70% of patients with neuropathic pain at baseline, report a clinically meaningful improvement in either pain intensity or LBLP-related disability four months after consulting in primary care. This suggests the majority of patients with neuropathic pain who consult in primary care will have a good outcome despite the beliefs that neuropathic pain is persistent and difficult to treat. It is commonly perceived that neuropathic pain has a tendency to be persistent, but over 50% of

patients with neuropathic pain (based on s-LANSS) at baseline did not have persistent neuropathic pain by four months. Clinicians could use these data to reassure patients of the expected course of their condition over the next four months.

The clinical course of LBLP patients with neuropathic pain and the potential prognostic factors associated with future outcomes were similar to the broader group of LBP patients and indeed to the even broader group of patients with other MSK conditions (Green et al. 2018). The implication is that LBLP patients with neuropathic pain in primary care, in the absence of widespread or progressive neurological deficit should be treated, at least initially in the same way as LBP patients with no known cause. Patients should continue to be examined and given a diagnosis of sciatica when indicated and imaging should be reserved for those patients for whom the result is likely to change clinical management. Patients with neuropathic pain based on s-LANSS in this research were characterised as a more severe phenotype compared to those with neuropathic pain based on clinical diagnosis but there is insufficient evidence to suggest that routine use of s-LANSS in clinical practice would benefit patients. Despite clinical guidelines recommending neuropathic pain medication for patients considered to have neuropathic pain (based on sciatica) (NICE NG59 2016) evidence from this research suggests that these patients could be managed initially with non-pharmacological care with or without pain medication (in a similar way to the broader population of patients with LBP) before specific neuropathic pain medication is recommended.

10.5 Implications for future research

The research in Chapter 8 identified a sub-group of patients as having persistent neuropathic pain, half of these patients reported a clinically meaningful improvement in either pain intensity or LBLP-related disability at four months. The implication is that patients in this sub-group could benefit from earlier, more active treatment, however it was difficult to predict cases of persistent neuropathic pain using potential prognostic factors selected from clinical examination or self-report, limited in part because a larger sample size was needed for this type of analysis. The findings will inform the development of future cohort studies of neuropathic pain in this patient population in terms of: 1) sample size calculations since greater sample sizes may provide more robust estimates, 2) selection of potential prognostic factors, perhaps broadening these to include those that are considered biomarkers of inflammatory pain mechanisms or responses from QST (see Chapter 8, section 8.6.2.1 (page 297) for a discussion of potential prognostic factors of patients with persistent neuropathic pain. A further limitation of the research in this thesis was the use of a proxy (presence of pain below the knee at four months) to describe patients with persistent neuropathic pain based on a diagnosis of sciatica. Future prospective cohorts with this patient population with data collected from clinical examination including MRI at more than one time point would allow for further investigation of the change in presence of neuropathic pain over time and a more robust investigation of the usefulness of persistent neuropathic pain as a sub-group of patients with poor prognosis. In the future, the clinical value of identifying patients with persistent neuropathic pain may be evaluated by investigating whether more targeted treatment changes the long-term

clinical course of this sub-group of patients, but the first challenge is predicting cases of persistent neuropathic pain based on baseline characteristics that can be routinely collected in primary care.

This research challenges the current definitions used to identify patients with neuropathic pain. Sciatica is often thought to be neuropathic but in this research there were few differences between patients with sciatica with or without evidence of nerve root compression on MRI both at baseline and in terms of clinical course. S-LANSS identified a group of patients with severe pain but there was no evidence to suggest that underlying neuropathic pathophysiological mechanisms explained persistent neuropathic pain defined in this way. The focus of future neuropathic pain research should be to identify those patients who need more active treatment to help manage pain and symptoms of neuropathic pain whilst not over-treating those likely to improve. Stratified primary care for LBP patients with and without leg pain that matches treatment to the risk of LBP-related disability (Hill et al. 2011b, Foster et al. 2014) has been incorporated into UK clinical guidelines for LBP and sciatica (NICE NG59 2016). Stratified care for patients with sciatica may also be beneficial and is currently being investigated in a randomised trial (Foster et al. 2017). Evidence in this thesis suggests that stratified care for LBLP patients with neuropathic pain based on s-LANSS may be worth exploring further; this would involve agreeing matched treatments and comparing a model of stratified care versus usual care in a future clinical trial.

The research in Chapter 9 identified that approximately 30% of patients with neuropathic pain were prescribed neuropathic pain medication, four months before or

after consulting in primary care. However, patients with neuropathic pain improved with and without such medication but there was evidence of confounding by indication, statistical methods to account for unmeasured confounding (for example propensity scores) are indicated in future observational cohort designs with larger sample sizes. Future research investigating the prescribing patterns of specific neuropathic pain medications in primary care, the characteristics that predict which LBLP patients benefit from neuropathic pain medications, and qualitative research investigating the factors that influence prescribing practice of clinicians in primary care is indicated and may lead to future studies that test interventions that are either based on, or incorporate the use of, neuropathic pain medications.

10.6 Conclusions

Neuropathic LBLP in primary care is common, estimates of point prevalence varied from 48% to 74% depending on the method used to define neuropathic pain. Many patients diagnosed with sciatica did not have neuropathic pain defined using s-LANSS. At baseline, LBLP-related morbidities such as depression, anxiety and worse general health were more common in patients with neuropathic pain based on s-LANSS compared to those with neuropathic pain based on sciatica. The clinical course of patients showed rapid improvements up to four months after baseline consultation across all three definitions of neuropathic pain with minimal improvement thereafter; the extent of improvement depended on the approach used to define cases. The presence of neuropathic pain was not always associated with poor prognosis. The presence of neuropathic pain (based on s-LANSS) changed over time, most commonly

by four months follow-up. The clinical course over three years of patients with persistent neuropathic pain at four months, based on two definitions, s-LANSS and clinical diagnosis of sciatica, was worse compared to those with non-persistent neuropathic pain. There was no evidence that factors from neurological examination were associated with persistent neuropathic pain at four months, there was more, although limited evidence that prognostic factors known to be important in the broader group of LBP patients were associated with persistent neuropathic pain. Patients with neuropathic pain were commonly prescribed pain medication, approximately 30% of patients with neuropathic pain (across all three definitions) were prescribed neuropathic pain medication, similar proportions improved without such medication. The research carried out informs clinical practice of the nature of neuropathic pain. It challenges the current perceptions that: sciatica is always a neuropathic pain condition, patients with neuropathic pain do worse over time compared with those without, and neuropathic pain is always persistent. The challenge in predicting cases of persistent neuropathic pain is highlighted with findings able to inform future research that attempts to better understand this.

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Appendix A Supplementary data for Chapter Three

Appendix A1 Full systematic search strategy

Full details of search strategy used in Medline using the interface HDAS (number of results for each search term are denoted at the end of each line)

	Search term
LBLP	1. Medline; Exp BACK PAIN/; 30077 results.
	2. Medline; (Backache OR "back ache").ti,ab; 2163 results.
	3. Medline; lumbago.ti,ab; 1177 results.
	4. Medline; ((spine OR spinal) adj3 pain).ti,ab; 6171 results.
	5. Medline; ((spine OR spinal) adj3 disorder*).ti,ab; 2970 results.
	6. Medline; exp INTERVERTEBRAL DISC DEGENERATION/ OR exp INTERVERTEBRAL DISC DISPLACEMENT/ OR exp SPINAL STENOSIS/ OR exp SPONDYLITIS/ OR exp SPONDYLOSIS/; 51862 results.
	7. Medline; (spondylitis OR spondylo*).ti,ab; 25254 results.
	8. Medline; ((slip* OR prolapse* OR herniat* OR intervertebral OR bulg* OR sequestration) adj3 (disc OR disk)).ti,ab; 15539 results.
	9. Medline; ((((spine OR spinal OR foramin* OR central OR canal) adj3 (stenosis OR stenotic)))).ti,ab; 5943 results.
	10. Medline; ((back adj3 pain)).ti,ab; 34366 results.
	11. Medline; (leg adj3 pain).ti,ab; 4465 results.
	12. Medline; 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11; 115228 results.
Neuropathic pain	13. Medline; Exp PERIPHERAL NERVOUS SYSTEM DISEASES/; 145789 results.
	14. Medline; "painDETECT".ti,ab; 77 results.
	15. Medline; "Douleur Neuropathique en 4 question*".ti,ab; 12 results.
	16. Medline; LANSS.ti,ab; 91 results.

	17. Medline; S-LANSS.ti,ab; 28 results. 18. Medline; ((((neur* OR nerv*) adj6 (compress* OR damag* OR injur* OR symptom*)))).ti,ab; 137013 results. 19. Medline; (((((neur* OR nerv*) adj3 (pain* OR discomfort* OR system*))))).ti,ab; 273367 results. 20. Medline; 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19; 498012 results.
Radicular pain or sciatica	21. Medline; ((radiculopath* OR radiculitis OR (radicular adj3 syndr*))).ti,ab; 5510 results. 22. Medline; RADICULOPATHY/ OR SCIATICA/; 7889 results. 23. Medline; sciatica.ti,ab; 3525 results. 24. Medline; 21 OR 22 OR 23; 12760 results.
(LBLP) and (neuropathic pain), or (radicular pain or sciatica)	25. Medline; (12 AND 20) OR 24; 22454 results
Epidemiology 1	26. Medline; exp INCIDENCE/; 185434 results. 27. Medline; inciden*.ti,ab; 631470 results. 28. Medline; exp PREVALENCE/; 203571 results. 29. Medline; prevalen*.ti,ab; 495302 results. 30. Medline; exp EPIDEMIOLOGY/; 36504 results. 31. Medline; epidemiol*.ti,ab; 277423 results. 32. Medline; exp PROGNOSIS/; 1169144 results. 33. Medline; exp DISEASE PROGRESSION/; 127594 results. 34. Medline; prognos*.ti,ab; 399860 results. 35. Medline; determinant*.ti,ab; 173284 results. 36. Medline; characteristic*.ti,ab; 950207 results. 37. Medline; factor*.ti,ab; 2359489 results.

	38. Medline; prevalen*.ti,ab; 495302 results.
	39. Medline; course.ti,ab; 438089 results.
	40. Medline; indicator*.ti,ab; 189297 results.
	41. Medline; subgroup* OR sub-group*.ti,ab; 152928 results.
	42. Medline; long-term.ti,ab; 560737 results.
	43. Medline; rate*.ti,ab; 2022693 results.
	44. Medline; occurrence*.ti,ab; 262047 results.
	45. Medline; progress*.ti,ab; 774215 results.
	46. Medline; predict*.ti,ab; 1020175 results.
	47. Medline; mediat*.ti,ab; 993432 results.
	48. Medline; model*.ti,ab; 1869597 results.
	49. Medline; risk.ti,ab; 1343317 results.
Epidemiology 2	50. Medline; exp CROSS-SECTIONAL STUDIES/; 193842 results.
	51. Medline; "cross section*".ti,ab; 220058 results.
	52. Medline; exp COHORT STUDIES/; 1434244 results.
	53. Medline; cohort.ti,ab; 282637 results.
	54. Medline; follow-up.ti,ab; 659459 results.
	55. Medline; exp CASE-CONTROL STUDIES/; 718545 results.
	56. Medline; retrospective.ti,ab; 309410 results.
	57. Medline; ("case control" OR "case controlled").ti,ab; 86481 results.
	58. Medline; prospective.ti,ab; 383341 results.
	59. Medline; (study OR studies).ti,ab; 6680769 results.
	60. Medline; ((patient* OR medical) adj3 (record* OR review* OR history*)).ti,ab; 293578 results.
	61. Medline; longitudinal.ti,ab; 153418 results.
	62. Medline; observation*.ti,ab; 640284 results.
	63. Medline; "time series".ti,ab; 17523 results.

	64. Medline; inception.ti,ab; 9119 results. 65. Medline; 50 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57 OR 58 OR 59 OR 60 OR 61 OR 62 OR 63 OR 64; 8033978 results.
Epidemiology 1	66. Medline; 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 29; 9255561 results.
Epidemiology 1 and 2	67. Medline; 65 AND 66; 4875935 results
Epidemiology of neuropathic pain in LBLP, sciatica and radicular pain.	68. Medline; 25 AND 67; 7479 results.
Limited to humans only.	69. Medline; 68 [Limit to: Humans]; 6250 results.

Full details of search strategy used in CINAHL using the interface HDAS

	Search term
LBLP	1. CINAHL; exp BACK PAIN/; 16150 results. 2. CINAHL; ((Backache OR "back ache")).ti,ab; 166 results. 3. CINAHL; lumbago.ti,ab.; 34 results. 4. CINAHL; (((spine OR spinal) adj3 pain)).ti,ab; 1603 results. 5. CINAHL; (((spine OR spinal) adj3 disorder*)).ti,ab; 652 results. 6. CINAHL; exp INTERVERTEBRAL DISK DISPLACEMENT/; 1847 results. 7. CINAHL; exp SPONDYLOSIS/; 842 results. 8. CINAHL; ((spondylitis OR spondylo*)).ti,ab; 2716 results. 9. CINAHL; (((slip* OR prolapse* OR herniat* OR intervertebral OR bulg* OR sequestration) adj3 (disc OR disk))).ti,ab; 1761 results.

	10. CINAHL; (((spine OR spinal OR foramin* OR central OR canal) adj3 (stenosis OR stenotic))).ti,ab; 988 results. 11. CINAHL; ((back adj3 pain)).ti,ab; 12896 results. 12. CINAHL; ((leg adj3 pain)).ti,ab; 1062 results. 13. CINAHL; 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12; 25526 results.
Neuropathic pain	14. CINAHL; exp PERIPHERAL NERVOUS SYSTEM DISEASES/; 19728 results. 15. CINAHL; "painDETECT" OR "Douleur Neuropathique en 4 question*" OR "S-LANSS" OR "LANSS".ti,ab; 85 results. 16. CINAHL; (((neur* OR nerv*) adj6 (compress* OR damag* OR injur* OR symptom))).ti,ab; 9740 results. 17. CINAHL; (((neur* OR nerv*) adj3 (pain* OR discomfort* OR system*))).ti,ab; 14443 results. 18. CINAHL; 14 OR 15 OR 16 OR 17; 39144 results.
Radicular pain or sciatica	19. CINAHL; ((radiculopath* OR radiculitis OR (radicular adj3 syndr*))).ti,ab; 963 results. 20. CINAHL; exp RADICULOPATHY/; 938 results. 21. CINAHL; exp SCIATICA/; 670 results. 22. CINAHL; sciatica.ti,ab.; 525 results. 23. CINAHL; 19 OR 20 OR 21 OR 22; 2187 results.
(LBLP) and (neuropathic pain), or (radicular pain or sciatica)	24. CINAHL; (13 AND 19) OR 23; 3584 results.
Epidemiology 1	25. CINAHL; exp INCIDENCE/; 24827 results. 26. CINAHL; inciden*.ti,ab.; 65811 results. 27. CINAHL; exp PREVALENCE/; 31602 results. 28. CINAHL; exp EPIDEMIOLOGY/; 303541 results. 29. CINAHL; prevalen*.ti,ab.; 67951 results.

	30. CINAHL; epidemiol*.ti,ab.; 28925 results.
	31. CINAHL; exp PROGNOSIS/; 159718 results.
	32. CINAHL; exp DISEASE PROGRESSION/; 17336 results.
	33. CINAHL; prognos*.ti,ab.; 27178 results.
	34. CINAHL; determinant*.ti,ab.; 15748 results.
	35. CINAHL; characteristic*.ti,ab.; 81818 results.
	36. CINAHL; factor*.ti,ab.; 214771 results.
	37. CINAHL; course.ti,ab.; 38784 results.
	38. CINAHL; indicator*.ti,ab.; 22523 results.
	39. CINAHL; ((subgroup* OR sub-group*)).ti,ab; 17372 results.
	40. CINAHL; long-term.ti,ab.; 65064 results.
	41. CINAHL; rate*.ti,ab.; 179131 results.
	42. CINAHL; occurrence*.ti,ab.; 17366 results.
	43. CINAHL; progress*.ti,ab.; 59097 results.
	44. CINAHL; predict*.ti,ab.; 113883 results.
	45. CINAHL; mediat*.ti,ab; 29586 results.
	46. CINAHL; model*.ti,ab.; 156915 results.
	47. CINAHL; risk.ti,ab; 229499 results.
	48. CINAHL; 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47; 1038657 results.
Epidemiology 2	49. CINAHL; exp CROSS SECTIONAL STUDIES/; 70011 results.
	50. CINAHL; "cross section*".ti,ab; 41389 results.
	51. CINAHL; exp PROSPECTIVE STUDIES/; 175309 results.
	52. CINAHL; exp RETROSPECTIVE DESIGN/; 82281 results.
	53. CINAHL; cohort.ti,ab; 52533 results.
	54. CINAHL; follow-up.ti,ab; 75826 results.
	55. CINAHL; retrospective.ti,ab.; 39964 results.
	56. CINAHL; prospective.ti,ab.; 57697 results.

	57. CINAHL; exp CASE CONTROL STUDIES/; 33440 results. 58. CINAHL; ("case control" OR "case controlled").ti,ab; 10422 results. 59. CINAHL; (study OR studies).ti,ab; 658359 results. 60. CINAHL; longitudinal.ti,ab; 26986 results. 61. CINAHL; (((patient* OR medical) adj3 (record* OR review* OR history*))).ti,ab; 40575 results. 62. CINAHL; exp OBSERVATIONAL METHODS/; 14793 results. 63. CINAHL; observation.ti,ab; 16920 results. 64. CINAHL; inception.ti,ab; 2249 results. 65. CINAHL; "time series".ti,ab; 1888 results. 66. CINAHL; 49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57 OR 58 OR 59 OR 60 OR 61 OR 62 OR 63 OR 64 OR 65; 844747 results.
Epidemiology of neuropathic pain in LBLP, sciatica and radicular pain.	67. CINAHL; 48 AND 66; 574315 results. 68. CINAHL; 24 AND 67; 1449 results.

B1.3 Full details of search strategy used in AMED using the interface OVID

	Search term
LBLP	1. exp backache/ 2. (Backache or "back ache").ti,ab. 3. lumbago.ti,ab. 4. ((spine or spinal) adj3 pain).ti,ab. 5. ((spine or spinal) adj3 disorder*).ti,ab. 6. exp intervertebral disk degeneration/ or exp intervertebral disk hernia/ or exp vertebral canal stenosis/ or exp spondylitis/ or exp spondylosis/ 7. (spondylitis or spondylo*).ti,ab.

	8. ((slip* or prolapse* or herniat* or intervertebral or bulg* or sequestration) adj3 (disc or disk)).ti,ab. 9. ((spine or spinal or foramin* or central or canal) adj3 (stenosis or stenotic)).ti,ab. 10. (back adj3 pain).ti,ab. 11. (leg adj3 pain).ti,ab. 12. or/1-11
Neuropathic pain	13. exp peripheral neuropathy/ 14. "painDETECT".ti,ab. 15. "Douleur Neuropathique en 4 question*".ti,ab. 16. "S-LANSS".ti,ab. 17. "LANSS".ti,ab. 18. ((neur* or nerv*) adj6 (compress* or damag* or injur* or symptom*)).ti,ab. 19. ((neur* or nerv*) adj3 (pain* or discomfort* or system*)).ti,ab. 20. or/13-19
Radicular pain or sciatica	21. (radiculopath* or radiculitis or (radicular adj3 syndr*)).ti,ab. 22. exp radiculopathy/ or exp sciatica/ 23. sciatica.ti,ab. 24. or/21-23
(LBLP) and (neuropathic pain), or (radicular pain or sciatica)	25. (12 and 20) or 24
Epidemiology 1	26. exp incidence/ 27. inciden*.ti,ab. 28. exp prevalence/ 29. prevalen*.ti,ab. 30. exp epidemiology/

	31. epidemiol*.ti,ab. 32. exp prognosis/ 33. exp disease course/ 34. prognos*.ti,ab. 35. determinant*.ti,ab. 36. characteristic*.ti,ab. 37. factor*.ti,ab. 38. course.ti,ab. 39. indicator*.ti,ab. 40. (subgroup* or sub-group*).ti,ab. 41. long-term.ti,ab. 42. rate*.ti,ab. 43. occurrence*.ti,ab. 44. progress*.ti,ab. 45. predict*.ti,ab. 46. mediat*.ti,ab. 47. model*.ti,ab. 48. risk.ti,ab. 49. or/26-48
Epidemiology 2	50. exp Epidemiologic methods/ 51. exp cross-sectional study/ 52. cohort.ti,ab. 53. follow-up.ti,ab. 54. retrospective.ti,ab. 55. ("case control" or "case controlled").ti,ab. 56. prospective.ti,ab. 57. (study or studies).ti,ab. 58. ((patient* or medical) adj3 (record* or review* or history*)).ti,ab.

	59. longitudinal.ti,ab. 60. observation*.ti,ab. 61. "time series".ti,ab. 62. inception.ti,ab. 63. or 50-62
Epidemiology 1 and 2	64. 49 and 63
Epidemiology of neuropathic pain in LBLP, sciatica and radicular pain.	65. 25 and 64
Limited to humans only.	66. limit 65 to human

Full details of search strategy used in EMBASE using the interface OVID

	Search term
LBLP	1. exp backache/ 2. (Backache or "back ache").ti,ab. 3. lumbago.ti,ab. 4. ((spine or spinal) adj3 pain).ti,ab. 5. ((spine or spinal) adj3 disorder*).ti,ab. 6. exp intervertebral disk degeneration/ or exp intervertebral disk hernia/ or exp vertebral canal stenosis/ or exp spondylitis/ or exp spondylosis/ 7. (spondylitis or spondylo*).ti,ab. 8. ((slip* or prolapse* or herniat* or intervertebral or bulg* or sequestration) adj3 (disc or disk)).ti,ab. 9. ((spine or spinal or foramin* or central or canal) adj3 (stenosis or stenotic)).ti,ab. 10. (back adj3 pain).ti,ab.

	11. (leg adj3 pain).ti,ab. 12. or/1-11
Neuropathic pain	13. exp peripheral neuropathy/ 14. "painDETECT".ti,ab. 15. "Douleur Neuropathique en 4 question*".ti,ab. 16. "S-LANSS".ti,ab. 17. "LANSS".ti,ab. 18. ((neur* or nerv*) adj6 (compress* or damag* or injur* or symptom*)).ti,ab. 19. ((neur* or nerv*) adj3 (pain* or discomfort* or system*)).ti,ab. 20. or/13-19
Radicular pain or sciatica	21. (radiculopath* or radiculitis or (radicular adj3 syndr*)).ti,ab. 22. exp radiculopathy/ or exp sciatica/ 23. sciatica.ti,ab. 24. or/21-23
(LBLP) and (neuropathic pain), or (radicular pain or sciatica)	25. (12 and 20) or 24
Epidemiology 1	26. exp incidence/ 27. inciden*.ti,ab. 28. exp prevalence/ 29. prevalen*.ti,ab. 30. exp epidemiology/ 31. epidemiol*.ti,ab. 32. exp prognosis/ 33. exp disease course/ 34. prognos*.ti,ab. 35. determinant*.ti,ab.

	36. characteristic*.ti,ab.
	37. factor*.ti,ab.
	38. course.ti,ab.
	39. indicator*.ti,ab.
	40. (subgroup* or sub-group*).ti,ab.
	41. long-term.ti,ab.
	42. rate*.ti,ab.
	43. occurrence*.ti,ab.
	44. progress*.ti,ab.
	45. predict*.ti,ab.
	46. mediat*.ti,ab.
	47. model*.ti,ab.
	48. risk.ti,ab.
	49. or/26-48
Epidemiology 2	50. exp cross-sectional study/
	51. "cross section*".ti,ab.
	52. exp cohort analysis/
	53. cohort.ti,ab.
	54. follow-up.ti,ab.
	55. exp case control study/
	56. retrospective.ti,ab.
	57. ("case control" or "case controlled").ti,ab.
	58. prospective.ti,ab.
	59. (study or studies).ti,ab.
	60. ((patient* or medical) adj3 (record* or review* or history*)).ti,ab.
	61. longitudinal.ti,ab.
	62. observation*.ti,ab.
	63. "time series".ti,ab.

	64. inception.ti,ab.
Epidemiology 1 and 2	65. or/50-64 66. 49 and 65
Epidemiology of neuropathic pain in LBLP, sciatica and radicular pain.	67. 25 and 66
Limited to humans only.	68. limit 67 to human

Full details of search strategy used in Web of Science using the interface OVID

		Search term
LBLP	#1	TOPIC: ((Backache or "back ache"))
	#2	TS= lumbago
	#3	TS=((spine or spinal) NEAR/3 pain)
	#4	TS=((spine or spinal) NEAR/3 disorder*)
	#5	TS= (spondylitis or spondylo*)
	#6	TS=((slip* or prolapse* or herniat* or intervertebral or bulg* or sequestration) NEAR/3 (disc or disk))
	#7	TS= ((spine or spinal or foramin* or central or canal) NEAR/3 (stenosis or stenotic)).
	#8	TS= (back NEAR/3 pain).
	#9	TS= (leg NEAR/3 pain)
	#10	#9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
Neuropathic pain	#11	TS="painDETECT"
	#12	TS="Douleur Neuropathique en 4 question*".
	#13	TS="S-LANSS"
	#14	TS="LANSS"

	#15 TS=((neur* or nerv*) NEAR/6 (compress* or damag* or injur* or symptom*)) #16 TS=((neur* or nerv*) NEAR/3 (pain* or discomfort* or system*)) #17 #16 OR #15 OR #14 OR #13 OR #12 OR #11
Radicular pain or sciatica	#18 TS=(radiculopath* or radiculitis or (radicular NEAR/3 syndr*)). #19 TS=sciatica
(LBLP) and (neuropathic pain), or (radicular pain or sciatica)	#20 #19 OR #18
Epidemiology 1	#21 TS=(inciden* OR prevalen* OR epidemiol* OR prognos* OR determinant* OR characteristic* OR factor* OR course OR (subgroup* or sub-group*) OR (long-term) OR rate* OR occurrence* OR progress* OR predict* OR mediat* OR model* OR risk*)
Epidemiology 2	#22 TS=((cross-section* OR "cross section") OR cohort OR follow-up OR retrospective OR ("case control" or "case controlled") OR prospective OR (study or studies) OR ((patient* or medical) NEAR/3 (record* or review* or history*)) OR longitudinal OR observation* OR "time series" OR inception)
Epidemiology of neuropathic pain in LBLP, sciatica and radicular pain.	#23 #17 AND #10 #24 #23 OR #20 #25 #22 AND #21 #26 #25 AND #24

Full details of search strategy used in TRIP database

	Search term
LBLP	sciatica or back pain or leg pain

Neuropathic pain	neuropathic pain
Epidemiology	prevalence or characteristics or prognosis or epidemiology

Appendix A2 Data extraction tool

Reviewer	(please circle) SS/KD/KK
Author and year	
Title	

Where domains are not reported please report as N/A.

Study description	
Study design (longitudinal or cross sectional, or includes data of both types.)	
Study population	
Country of origin	
Setting (physiotherapy outpatients, general practice, osteopathic or chiropractic clinics,	

neurology/neurosurgery, orthopaedics, pain clinic)	
Definition of low back pain, with or without leg pain defined for population in study.	
Inclusion criteria	
Exclusion criteria	
Methods and sampling	

Methods of recruiting sample (eg phone, mail, consecutive clinic patients)	
Is sample size large enough to estimate prevalence with adequate precision? (eg, was a sample size calculation reported?)	
Number of invited participants in study sample.	
Number of participants in final sample size.	
Response rate (eg % returned questionnaires, complete data sets).	
How was neuropathic pain diagnosed or defined? Give details: by history taking, clinical examination, pharmalogical diagnostic approach or using questionnaire	

tool (LANSS, S-LANSS, DN4, Pain Detect or other) If more than one method used specify each method.	
Was neuropathic pain AND other measurements carried out in a valid and reliable manner? (eg were measurements blind?).	
3.1 Complete for longitudinal data	
Primary time points at which measurements taken (record in months, years).	
Attrition (% drop outs)	
Characteristics of the population. (i.e. independent variables that may be investigated for prognostic value)	
Age (mean +/- range)	
Sex ratio of participants (%M)	
Episode duration of LBP/ leg pain. Consider, current episode for LBP/	

leg pain and time since ‘pain free month’ if reported.	
Pain intensity. Consider, current, average and ‘least’ pain for both back and leg pain. VAS or NRS.	
Other baseline characteristics of interest. Eg, proportion of the population who have had surgery.	
Results	
5.1 Complete for longitudinal data	
Longitudinal data: Evidence of incidence and associated prognostic factors between neuropathic pain and low back pain with or without leg pain. (Crude estimates of RR and multivariate model if available).	
5.2 Complete for cross sectional data	
Evidence of prevalence of neuropathic pain in study population. (Include 95% confidence intervals if available).	

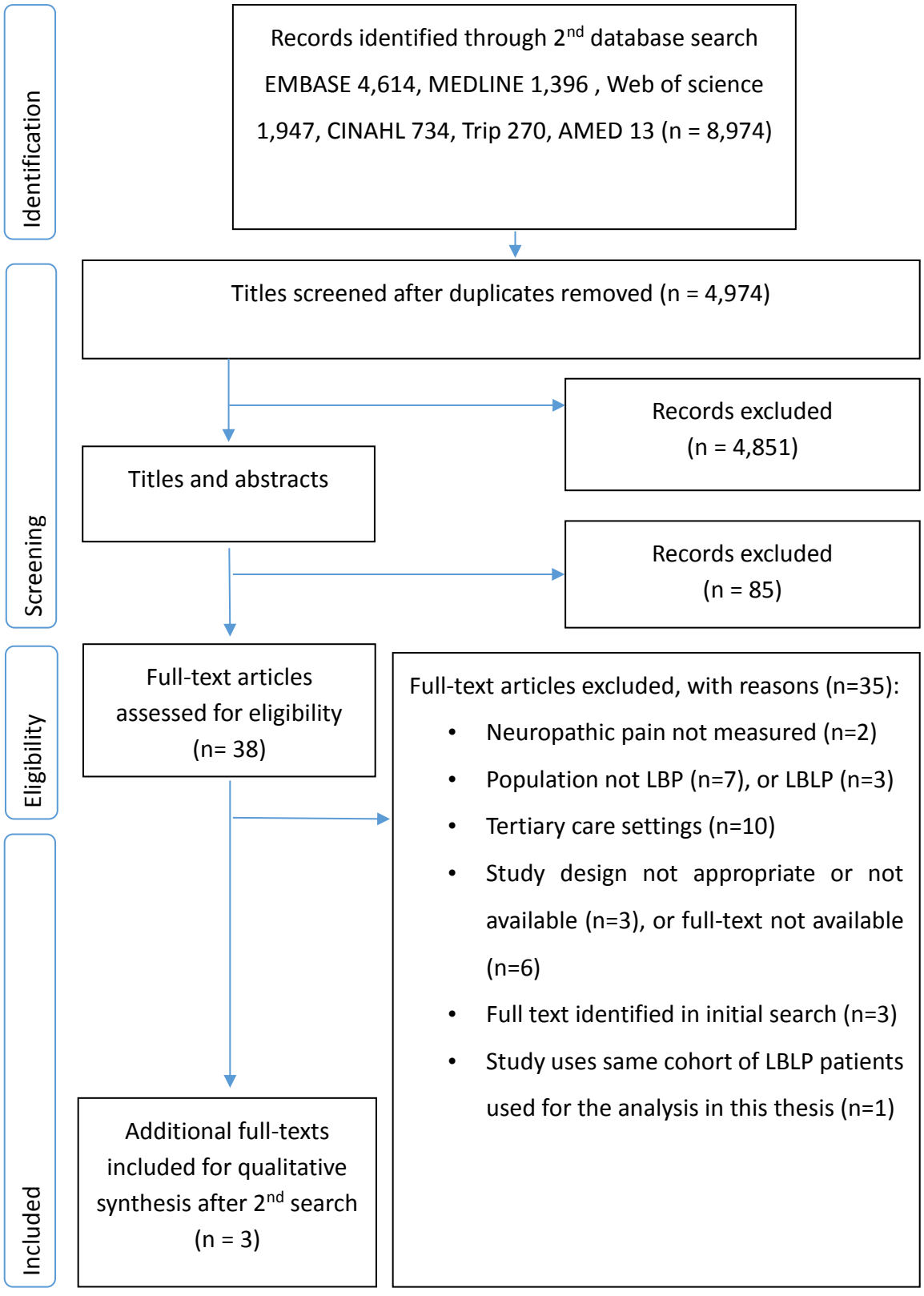
• Absolute numbers • Point prevalence • Period prevalence • Lifetime prevalence		
Cross-sectional data: Associations between outcomes of interest between neuropathic pain and low back pain with or without leg pain. (OR and multivariate	Pain (eg VAS/NRS/ current, average or least)	
	Disability (eg RMDQ or ODI)	

model if available, otherwise report as %, with p value).		
	General health (eg EQ5D, SF36) Psychological function (eg HADS) Others (eg PSEQ)	
	Other outcomes of interest: (eg % of pts with clinical characteristics common to neuropathic pain, eg allodynia,	

	burning pain as estimated for LANNS/ DN4 etc). Quantitative sensory testing (QST) profiles are not relevant to the study.	
Conclusions and limitations of study's methods/ results		
Authors conclusion/s		
Conflict of interest/ funding		
Reviewers comments		

Appendix A3 Flow chart of the 2nd systematic search and study selection

The initial search was updated in January 2018 (adapted from the PRISMA flow chart (Moher et al., 2009))



Appendix A4 Results of quality appraisal

Results of quality assessment (described as risk of bias) of the ten included studies used to derive prevalence

		Attal et al 2011	Beith et al 2011	Gierthmühlen et al 2017	Hüllemann et al 2016	Morsø et al 2011	Orita et al 2016	Ouédraogo et al 2012	Schafer et al 2011	Uher et al 2013	Walsh et al 2009
External validity	Target population	High	High	High	Low	High	High	High	High	High	High
	Sampling frame	Low	Low	High	Low	Low	High	High	Low	High	Low
	Random selection	Low	Low	High	Low	Low	Low	Low	Low	Low	Low
	Non-response bias	High	Low	High	Low	Low	High	High	High	High	High
Internal validity	Case definition (LBLP and neuropathic pain)	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
	Validity and reliability of neuropathic pain	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low

		Attal et al 2011	Beith et al 2011	Gierthmühlen et al 2017	Hüllemann et al 2016	Morsø et al 2011	Orita et al 2016	Ouédraogo et al 2012	Schafer et al 2011	Uher et al 2013	Walsh et al 2009
	Mode of data collection	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
	Appropriate prevalence period reported	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Analysis	Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Low	Low	High	Low	Low	Low	Low	Low	Low	Low
	Overall risk of bias	**Mod**	**Low**	**High**	**Low**	**Low**	**Mod**	**Mod**	**Mod**	**Mod**	**Mod**

Results of quality assessment (described as risk of bias) of the twelve included studies used to describe characteristics and prognosis

	Study participation	**Study Attrition**	**Prognostic Factor**	**Outcome**	**Confounding factor**	**Analysis**	**Overall risk of bias**
Beith et al 2011	Moderate	Not relevant	Low	Low	Moderate	Low	**Moderate**
Defrin et al 2014	Moderate	Not relevant	Moderate	Not relevant	Unsure	Unsure	**Moderate**
Freynhagen et al 2008	Moderate	Not relevant	Low	Moderate	Not relevant	Low	**Moderate**
Gierthmühlen et al 2017	Moderate	Not relevant	Low	Low	Not relevant	Low	**Low**
Hüllemann et al 2016	Low	High	Not relevant	Low	High	Unsure	**Moderate**
Mahn et al 2011	Low	Not relevant	Not relevant	Not relevant	Not relevant	Low	**Low**
Morsø et al 2011	Moderate	Low	Low	Low	Moderate	Low	**Moderate**

	Study participation	Study Attrition	Prognostic Factor	Outcome	Confounding factor	Analysis	Overall risk of bias
Schafer et al 2011	Low	Low	Moderate	Low	Low	Low	**Low**
Smart et al 2012	Low	Not relevant	Moderate	Moderate	Not relevant	Low	**Moderate**
Tutoglu et al 2014	Unsure	Not relevant	Low	Moderate	Not relevant	Moderate	**Moderate**
Uher and Bob 2013	High	Not relevant	Low	Low	Not relevant	Low	**Moderate**
Walsh et al 2009	Low	Not relevant	Low	Low	Not relevant	Low	**Low**

Appendix B Supplementary data for Chapter Seven: analysis based on imputed data

Proportion of patients with neuropathic pain (s-LANSS) at baseline and at three subsequent follow-up time-points

Time	**Proportion (%)**	**Confidence Interval (95%)** *
Baseline	48.4	44.4 to 52.4
Four months	26.2	22.0 to 30.4
Twelve months	24.8	20.5 to 29.1
Three years	22.7	17.3 to 26.1

*Confidence intervals are for certainty around a point estimate for imputed data.

Change in the presence of neuropathic pain in patients over a three year follow-up period

Presence or absence of neuropathic pain over three years*				**Proportion (%)**	**Confidence Interval (95%)** †	**Sub-group**
Base-line	4 months	12 months	3 years			
0	0	0	0	38.2	33.8 to 42.6	Non-neuropathic
0	0	0	1	3.6	1.5 to 5.7	Developing
0	0	1	0	3.3	1.5 to 5.5	Developing
0	0	1	1	1.0	0.0 to 2.1	Developing
0	1	0	0	2.4	0.1 to 3.9	Developing
0	1	0	1	0.7	0.6 to 1.6	Developing
0	1	1	0	1.3	0.2 to 2.5	Developing
0	1	1	1	1.1	0.0 to 2.0	Developing
1	0	0	0	18.3	14.7 to 22.0	Non-persistent
1	0	0	1	3.7	1.7 to 5.7	Non-persistent
1	0	1	0	3.7	1.6 to 5.7	Non-persistent
1	0	1	1	2.1	0.6 to 3.6	Longstanding persistent
1	1	0	0	5.6	3.3 to 8.0	Non-persistent
1	1	0	1	2.6	0.8 to 4.4	Longstanding persistent
1	1	1	0	5.5	3.3 to 7.8	Longstanding persistent
1	1	1	1	6.8	4.3 to 9.4	Longstanding persistent

Abbreviation: s-LANSS, self-report version of the Leeds Assessment of Neuropathic Symptoms and signs neuropathic pain scale

*0 indicates s-LANSS score < 12 (non-neuropathic pain), 1 indicates s-LANSS score ≥ 12 (possible neuropathic pain)

†Confidence intervals are for certainty around a point estimate for imputed data.

Proportion of patients by neuropathic pain sub-group

Sub-group*	Proportion (%)	Confidence Interval (95%) †
Non-neuropathic pain	38.2	33.8 to 42.6
Non-persistent neuropathic pain	31.3	27.1 to 35.5
Longstanding persistent neuropathic pain	17.1	13.5 to 20.7
Developing neuropathic pain	13.4	10.0 to 20.7

Abbreviation: s-LANSS, self-report version of the Leeds Assessment of Neuropathic Symptoms and signs neuropathic pain scale

*Sub-groups: Non-neuropathic pain, s-LANSS < 12 at baseline and each follow-up point thereafter. Developing neuropathic pain, s-LANSS < 12 at baseline and ≥ 12 at one or more follow-up points. Non-persistent neuropathic pain, s-LANSS ≥ 12 at baseline and ≥ 12 at one (at most) of the three follow-up points. Longstanding persistent neuropathic pain, s-LANSS ≥ 12 at baseline and ≥ 12 at two or more of the three follow-up points.

†Confidence intervals are for certainty around a point estimate for imputed data.

Baseline characteristics of patients by neuropathic pain sub-group over three-years

Baseline characteristic	**Neuropathic pain sub-group[†] over three years**			
(shown as %, (95% confidence intervals) unless stated as mean)*	**Unchanged non-neuropathic pain (40.4%)**	**Neuropathic pain (non-persistent) (29.7%)**	**Longstanding persistent neuropathic pain (15.6%)**	**Developing neuropathic pain (14.3%)**
Sociodemographic characteristics				
Female	57.0 (50.4 to 63.6)	69.1 (61.8 to 76.4)	67.3 (56.6 to 78.0)	61.7 (49.7 to 73.8)
Age, mean	50.5 (48.6 to 52.4)	49.9 (47.7 to 52.0)	49.7 (46.7 to 52.8)	50.4 (46.8 to 54.0)
Socio-economic status: Routine and manual occupations, never worked and long-term unemployed	48.0 (41.2 to 54.8)	55.3 (47.5 to 63.1)	59.4 (47.8 to 71.1)	46.4 (33.6 to 59.2)
Pain characteristics				

Baseline characteristic		**Neuropathic pain sub-group[†] over three years**			
(shown as %, (95% confidence intervals) unless stated as mean)*		**Unchanged non-neuropathic pain (40.4%)**	**Neuropathic pain (non-persistent) (29.7%)**	**Longstanding persistent neuropathic pain (15.6%)**	**Developing neuropathic pain (14.3%)**
Leg pain intensity (0-10), mean		4.5 (4.2 to 4.8)	5.7 (5.3 to 6.0)	5.8 (5.3 to 6.4)	5.4 (4.8 to 6.0)
Leg pain worse		46.2 (39.5 to 52.9)	49.8 (42.0 to 57.6)	45.7 (34.4 to 56.9)	37.8 (34.4 to 56.9)
Pain location	Pain below the knee	64.1 (57.7 to 70.5)	75.9 (69.1 to 82.7)	80.7 (71.1 to 90.3)	67.1 (55.3 to 78.9)
	Pain in one leg	77.1 (71.5 to 82.7)	74.8 (67.9 to 81.7)	66.6 (55.9 to 77.4)	79.0 (69.0 to 89.0)
Duration of back pain symptoms in current episode	Less than 6 weeks	38.7 (32.1 to 45.3)	32.8 (25.8 to 39.8)	35.3 (25.3 to 45.2)	35.5 (23.7 to 47.4)
	6 to 12 weeks	21.3 (15.7 to 26.9)	24.9 (18.4 to 31.4)	17.4 (9.3 to 25.6)	13.9 (4.9 to 22.9)

Baseline characteristic		**Neuropathic pain sub-group[†] over three years**			
(shown as %, (95% confidence intervals) unless stated as mean)*		**Unchanged non-neuropathic pain (40.4%)**	**Neuropathic pain (non-persistent) (29.7%)**	**Longstanding persistent neuropathic pain (15.6%)**	**Developing neuropathic pain (14.3%)**
	> 3 months	40.0 (33.4 to 46.6)	41.2 (33.4 to 48.9)	45.5 (34.1 to 56.9)	55.1 (42.9 to 67.4)
Duration of leg pain symptoms in current episode	Less than 6 weeks	49.8 (43.0 to 56.6)	39.4 (32.0 to 46.7)	38.3 (28.2 to 48.4)	39.4 (27.6 to51.3)
	6 to 12 weeks	20.5 (14.9 to 26.0)	25.1 (18.5 to 31.7)	15.0 (6.8 to 23.2)	16.7 (7.4 to 26.0)
	> 3 months	29.3 (22.8 to 35.8)	35.3 (27.7 to 43.0)	45.3 (33.6 to 56.9)	48.2 (35.1 to 61.3)
Widespread pain		40.5 (33.6 to 47.3)	35.8 (28.4 to 43.2)	55.4 (44.3 to 66.4)	43.3 (30.9 to 55.8)
Limitations in activities and risk of persistent disabling pain					
RMDQ (0-23), mean		11.0 (10.2 to 11.7)	13.5 (12.7 to 14.4)	15.0 (13.8 to 16.2)	12.8 (11.5 to 14.2)

Baseline characteristic		**Neuropathic pain sub-group[†] over three years**			
(shown as %, (95% confidence intervals) unless stated as mean)*		**Unchanged non-neuropathic pain (40.4%)**	**Neuropathic pain (non-persistent) (29.7%)**	**Longstanding persistent neuropathic pain (15.6%)**	**Developing neuropathic pain (14.3%)**
Risk of persistent disabling pain (STarT Back)	Low risk	20.0 (14.7 to 25.4)	12.2 (7.3 to 17.2)	6.3 (0.8 to 11.8)	84.5 (0.8 to 16.1)
	Medium risk	50.6 (43.8 to 57.3)	44.4 (36.6 to 52.2)	37.7 (26.2 to 49.1)	51.8 (39.2 to 64.3)
	High risk	29.4 (23.1 to 35.7)	43.4 (35.5 to 51.3)	56.0 (44.5 to 67.6)	39.8 (27.5 to 52.0)
Psychological characteristics					
HADS (depression) (0-21), mean		5.2 (4.7 to 5.6)	6.8 (6.2 to 7.5)	8.7 (7.7 to 9.7)	6.1 (5.3 to 7.0)
PSEQ (0-60), mean[‡]		38.2 (36.4 to 40.0)	32.2 (29.9 to 34.4)	27.6 (24.4 to 30.9)	34.3 (30.9 to 37.7)
Neurological examination findings					

Baseline characteristic		**Neuropathic pain sub-group[†] over three years**			
(shown as %, (95% confidence intervals) unless stated as mean)*		**Unchanged non-neuropathic pain (40.4%)**	**Neuropathic pain (non-persistent) (29.7%)**	**Longstanding persistent neuropathic pain (15.6%)**	**Developing neuropathic pain (14.3%)**
Presence of muscle weakness[§]	5/5	14.3 (10.1 to 19.3)	23.8 (17.1 to 30.6)	16.0 (5.9 to 24.2)	12.1 (4.3 to 20.0)
	0 to 4/5	85.7 (81.1 to 90.4)	76.2 (69.7 to 82.7)	84.0 (78.6 to 92.1)	87.9 (80.1 to 95.7)
Reflex change	None	85.6 (80.9 to 90.3)	78.3 (72.0 to 84.5)	71.6 (61.9 to 81.2)	82.1 (72.9 to 91.4)
	Slightly reduced	3.3 (0.9 to 5.8)	5.2 (1.9 to 8.6)	8.7 (2.9 to 14.4)	4.0 (-0.8 to 8.9)
	Significantly reduced or absent	11.1 (6.8 to 15.3)	16.5 (10.8 to 22.1)	19.8 (11.3 to 28.2)	13.8 (5.4 to22.1)

Baseline characteristic	**Neuropathic pain sub-group[†] over three years**			
(shown as %, (95% confidence intervals) unless stated as mean)*	**Unchanged non-neuropathic pain (40.4%)**	**Neuropathic pain (non-persistent) (29.7%)**	**Longstanding persistent neuropathic pain (15.6%)**	**Developing neuropathic pain (14.3%)**
Reduction or loss of sensation to pin-prick	33.8 (27.4 to 40.2)	46.9 (38.9 to 54.9)	51.4 (39.3 to 63.5)	41.5 (29.0 to 54.0)
Presence of allodynia or hyperalgesia[‖]	4.7 (1.8 to 7.7)	12.2 (7.0 to 17.5)	15.9 (7.4 to 24.4)	10.4 (3.0 to 17.7)
Neural tension test (any positive test) [**]	51.9 (45.4 to 58.4)	55.9 (48.3 to 63.5)	57.6 (46.7 to 68.6)	59.1 (47.6 to 70.6)
Pins and needles	30.6 (24.6 to 30.6)	70.8 (63.5 to 78.2)	77.4 (67.3 to 87.5)	32.1 (21.2 to 78.2)
Other definitions of neuropathic pain				
Clinical diagnosis of sciatica[††]	69.8 (63.7 to 76.0)	78.2 (71.7 to 84.7)	80.5 (71.2 to 89.8)	71.5 (60.2 to 82.8)
Neuroimaging				

Baseline characteristic	**Neuropathic pain sub-group[†] over three years**			
(shown as %, (95% confidence intervals) unless stated as mean)*	**Unchanged non-neuropathic pain (40.4%)**	**Neuropathic pain (non-persistent) (29.7%)**	**Longstanding persistent neuropathic pain (15.6%)**	**Developing neuropathic pain (14.3%)**
Evidence of nerve root compression on MRI	52.4 (45.3 to 59.4)	50.3 (42.4 to 58.1)	57.7 (46.1 to 69.2)	60.3 (47.4 to 73.3)

Abbreviations: HADS, Hospital Anxiety and Depression scale. MRI, magnetic resonance imaging. PSEQ, Pain Self-Efficacy Questionnaire. RMDQ, Roland Morris Disability Questionnaire (RMDQ) leg version. s-LANSS, self-report version of the Leeds Assessment of Neuropathic Symptoms and signs neuropathic pain scale

† Sub-groups: Non-neuropathic pain, s-LANSS < 12 at baseline and each follow-up point thereafter. Developing neuropathic pain, s-LANSS < 12 at baseline and ≥ 12 at one or more follow-up points. Non-persistent neuropathic pain, s-LANSS ≥ 12 at baseline and ≥ 12 at one (at most) of the three follow-up points. Longstanding persistent neuropathic pain, s-LANSS ≥ 12 at baseline and ≥ 12 at two or more of the three follow-up points.

*Confidence intervals are for certainty around a point estimate for imputed data

‡Higher scores on PSEQ reflect stronger self-efficacy belief

§ Muscle strength was tested according to the oxford scale and muscle weakness was categorised as 0-4 on this scale:

0. No visible flicker of movement or contraction
1. Flicker of movement
2. Full active movement with gravity counterbalanced
3. Full active movement against gravity but not applied resistance
4. Full active movement against gravity and some applied resistance
5. Full active movement against gravity and strong resistance

Muscle strength is reported as either normal (5/5) or reduced (0/5 to 4/5) as there were no observations for some categories and imputation was not possible

|| Hyperalgesia is an increased pain response to painful stimuli. Allodynia is pain response to non-painful stimuli (for example, strokes)

** Neural tension tests; straight leg raise, crossover straight leg raise, femoral stretch and slump test

††LBLP patients with a clinical diagnosis of sciatica are described as having “possible” neuropathic pain

Appendix C Supplementary data for Chapter Nine: analysis based on imputed data

Proportion of patients with improvement by neuropathic pain definition in those who were prescribed one or more neuropathic pain medications compared to those who were not.

Neuropathic pain medication‡	**Neuropathic pain definition**	**Patients with improvement* at four months**	
		Proportion (%)	***95% Confidence Interval†***
None	S-LANSS	68.3	60.5 to 76.0
	Clinical diagnosis of sciatica	71.5	65.7 to 77.2
	Clinical diagnosis of sciatica with evidence of nerve root compression	72.0	64.3 to 79.7
	Persistent neuropathic pain at four months†	40.0	24.4 to 55.6
One	S-LANSS	60.6	47.6 to 73.7
	Clinical diagnosis of sciatica	65.2	54.5 to 75.8
	Clinical diagnosis of sciatica with evidence of nerve root compression	66.0	52.5 to 79.6
	Persistent neuropathic pain at four months	47.6	25.3 to 69.9
Two or more	S-LANSS	50.8	31.0 to 70.6
	Clinical diagnosis of sciatica	53.5	38.8 to 68.3

Neuropathic pain medication‡	Neuropathic pain definition	Patients with improvement* at four months	
		Proportion (%)	***95% Confidence Interval†***
	Clinical diagnosis of sciatica with evidence of nerve root compression	51.4	33.5 to 69.4
	Persistent neuropathic pain at four months	36.3	6.0 to 66.7

Abbreviations: s-LANSS, self-report version of the Leeds Assessment of Neuropathic Symptoms and signs neuropathic pain scale

*Improvement: Leg pain intensity < 5 (0-10 NRS) or ≥ 30% reduction in LBLP-related disability (RMDQ 0-23) at 4 months

† Confidence intervals are for certainty around a point estimate for imputed data

‡ Neuropathic pain medications prescribed up to four months before and after an index consultation in the ATLAS research clinic

Persistent neuropathic pain: s-LANSS ≥ 12 at baseline and ≥ 12 at two or more of the three follow-up points

Definitions based on a clinical diagnosis of sciatica with evidence of nerve root compression are described as having “probable” neuropathic pain, those based on s-LANSS and sciatica (with or without evidence of nerve root compression) are described as having “possible” neuropathic pain.