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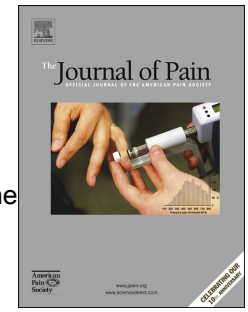

Neuropathic pain in low back-related leg pain patients: What is the evidence of prevalence, characteristics, and prognosis in primary care? A systematic review of the literature

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Running title:

Epidemiology of neuropathic pain in back and leg pain

Abstract

This systematic review synthesizes literature describing prevalence, characteristics and prognosis of low back-related leg pain (LBLP) patients with neuropathic pain in primary care and/or similar settings. Inclusion and exclusion criteria were developed and used by independent reviewers to screen citations for eligibility. The initial search yielded 24,948 citations; after screening 12 studies were included. Neuropathic pain was identified by case ascertainment tools (n=5), by clinical history with examination (n=4), and by LBLP samples assumed neuropathic (n=3). Neuropathic pain prevalence varied from 19% to 80%. There was consistent evidence for higher back-related disability (n=3), poorer health-related quality of life (n=2) and some evidence for more severe depression (n=2), anxiety (n=3) and pain intensity (n=4) in patients with neuropathic pain. Results were less consistent when cases were identified through clinical history plus examination than those identified using case ascertainment tools. Prognosis (n=1) of LBLP patients with neuropathic pain was worse compared to those without, in all outcomes (leg pain intensity, leg and back-related disability, self-reported general health) except back pain intensity. No studies described prognostic factors. This systematic review highlights the evidence gap in neuropathic pain in LBLP in primary care, especially with respect to prognosis.

Perspective

Patients with low back-related leg pain may have neuropathic pain. This systematic review emphasises the paucity of evidence describing the characteristics and prognosis of neuropathic pain in this patient population. Future research investigating prognosis of these

patients with neuropathic pain is likely to contribute to better understanding and management.

Key words

Low back pain; leg pain; primary care; neuropathic pain; epidemiology

1. Introduction

Neuropathic pain presents as one of the most challenging pain syndromes to identify and treat [52]. Patients with underlying neuropathic pain (considered to be pain caused by injury or disease to the somatosensory system [55]) commonly self-report neuropathic characteristics such as prickling and/or burning sensations, and heat and pressure induced pain. The International Association for the Study of Pain (IASP) developed a grading system to assist researchers and clinicians to identify cases of neuropathic pain [55]. The grading system proposes that a patient presenting with pain, and with a plausible clinical history together with relevant neurological examination findings, meets the criteria for a working hypothesis of possible neuropathic pain [55]. With the addition of appropriate findings from diagnostic tests, a patient can meet the criteria for probable neuropathic pain. When clinical examination is not possible in epidemiological research, (for example, Torrance et al [54] and VanDenKerfhof et al [60]) neuropathic case ascertainment tools use self-reported neuropathic characteristics (for example, Self-report version of Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) [8] to identify, at best, possible cases of neuropathic pain [20, 52].

Low back pain (LBP) is one of the most common presentations of neuropathic pain [9]. Regardless of underlying pain mechanisms, LBP is the leading cause of disability globally and a major public health problem [12]. Patients with leg pain related to their back pain (LBLP) is a common presentation of LBP with approximately two thirds of LBP patients seeking treatment in both primary and secondary care settings, reporting leg pain [32, 37]. LBLP is associated with increased disability and pain, and poorer quality of life compared to LBP

alone [31, 39]. There is a strong argument that research investigating the epidemiology of patients with LBP should distinguish those with LBLP based on their characteristics and prognosis [14, 23].

LBLP is clinically diagnosed as either sciatica (otherwise known as lumbar radicular pain) or referred leg pain. Sciatica is characterised by leg pain that often radiates to beyond the knee and into the foot or toes, it may be accompanied by muscle weakness and/or reflex change and/or pins and needles or numbness (paraesthesia), in a specific nerve root(s) distribution [36]. Sciatica is thought to be caused by compression of the spinal nerve root(s), most commonly by an intervertebral disc prolapse whereas referred leg pain is pain arising from structures in the back such as ligaments, discs or joints, but does not involve the spinal nerve(s). Mechanisms of pain are considered to be either neuropathic or if there is no injury or damage to the somatosensory system, the pain mechanism is deemed to be non-neuropathic and described by the term nociceptive. Currently, sciatica is considered neuropathic in nature and referred leg pain is considered nociceptive. However, there is evidence that the underlying mechanism of LBP and LBLP comprises coexisting neuropathic and nociceptive mechanisms [25], and that at times, sciatica patients may not present with neuropathic pain characteristics, and patients with referred leg pain might have neuropathic pain [40].

The first point of contact for individuals with back pain in the UK health care system, including those with neuropathic pain, are primary care providers [14]. The majority of these patients continue to be managed in primary rather than in secondary care [11] even if they complain of persistent and bothersome pain. Back pain patients consult in primary care seeking information and treatment options for their condition, these often include medication options and information on prognosis [11]. Primary care providers also act as gatekeepers, referring to specialist clinical settings only those patients who may require and/or benefit from specialist assessment and interventions. There is variation globally in access to primary care for individuals with back pain. Whilst patients in the UK are initially mainly seen by primary care providers, patients in other countries (depending on the structure of a country's health system) may have direct access to specialist centres (secondary care) as the first point of contact, including centres with neurosurgery, neurology and pain expertise, although they are likely very similar in presenting symptomatology to those patients not seen in specialist settings, at least initially. Research set in primary care and in other settings that patients have direct access to, is important as it is likely to capture the patient population seeking care with similar low back related pain problems [11].

Identification of mechanisms that underlie the development and persistence of back pain presentations, and the development of and testing of ways to better match treatment to patients, are both internationally agreed research priorities [14]. There are specific medication options for patients with neuropathic pain, based on underlying mechanisms that may

accompany nerve damage [20] and these are advocated for patients (including those with sciatica) consulting in primary care [43, 44]. Recognising neuropathic pain in LBLP patients in primary care is important as this may facilitate timely access to recommended medications, if deemed appropriate, which in turn may contribute to better outcomes for these patient. There have been attempts to identify neuropathic pain as a subgroup of LBP and LBLP [47, 48] and previous systematic reviews have addressed the broader area of neuropathic pain in LBP [19, 35]. Current pain research has predominantly been conducted in specialist pain centres often based in tertiary care. It is likely that populations of patients drawn from these settings are systematically different to patients in primary care and this may limit generalisability of these findings [16] to primary care consulters. 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. It is also not clear whether the characteristics of LBLP patients differ in patients with and without neuropathic pain. Currently, there are no published reviews summarising the research evidence on the epidemiology of neuropathic pain in LBLP. We conducted a systematic review of studies examining the prevalence, characteristics and prognosis of neuropathic pain in LBLP patients consulting in any setting that seemed to be the first point of contact for this population.

2. Methods

2.1. 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).

2.2. 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 for studies that fulfilled the inclusion and exclusion criteria (see Table 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, epidemiology, including key words and MeSH terms for prevalence and prognosis (see Supplementary Materials Table S1 for the full details of the search strategy used in MEDLINE). A supplementary search was carried out by bibliography screening and citation tracking of included studies [28], relevant systematic reviews and original studies of case identification tools [6, 9, 24]. 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.

2.3. Data extraction

All studies identified from the electronic databases were directly imported into online reference management (Endnote X7.4) and duplicates were removed. Eligible studies were

selected on title first by one reviewer (SH), then abstracts were screened 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 studies using a bespoke data extraction form on: study name, authors and publication year; publication language; study design; setting; 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; clinical course of condition and factors associated with prognosis. Authors were contacted for further data or clarification, where required.

2.4. Risk of bias (quality assessment)

Two quality assessment tools were used in this review [29, 34]. One to appraise the evidence on prevalence [34] and the other to appraise the evidence on characteristics and prognosis [29]. We used the tool developed by Hoy et al [34] to assess the risk of bias in prevalence studies; it includes ten items, four related to external validity (the assessment of whether the results of the study can be believed), and six related to internal validity (the assessment of how well the study is performed) (see supplementary materials Table S2). In this review, when information was insufficient to make a judgement 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 method of scoring the overall risk of study bias has been utilised by previous systematic reviews [2, 27, 58].

The Quality in Prognosis Studies (QUIPS) tool was used to appraise individual studies providing data on characteristics and prognosis (see supplementary materials Table S3). The reviewers assigned six different domains as having either 'low', 'moderate' or 'high' risk of bias or 'unsure of the risk of bias, or that the domain was not relevant. The study was then assigned as having an overall 'low', 'moderate' or 'high' risk of bias. All studies, regardless of their quality, were included for critical appraisal and synthesis. For both tools, two independent reviewers (SH and SS, KK or KD) completed the quality assessment and any disagreements were resolved by consensus.

2.5. Data analysis

Statistical pooling was not appropriate therefore a narrative synthesis was conducted with a description of studies and tabulation of results [1]. An exploration of the robustness of the synthesis, and of the relationships between and within studies, formed part of this narrative review.

3. Results

3.1. Studies identified

The search of electronic databases yielded 24,948 articles (Figure 1 shows a flow chart adapted from the PRISMA flow chart [41]). 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 1 summarises all reasons for excluded studies). Twelve full text articles were included in the final review and all underwent quality assessment and data extraction.

A summary of the included studies is presented in Table 2. 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 seven of the studies [3, 6, 42, 45, 46, 57, 62]. Ten studies reported on characteristics [6, 18, 25, 40, 42, 48, 51, 56, 57, 62], and from the two studies that provided longitudinal data [42, 48], it was possible to derive information on prognosis from one study [42]. A total of 3,457 patients were included in all twelve studies.

Overall, the sample sizes were small (the median sample size was 74). 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 [40, 51], and one study described characteristics with an alternative comparison group. Defrin et al [18] described neuropathic pain in LBLP patients with or without allodynia. These three studies were included in the review because of the relevance of the reported characteristics.

Neuropathic pain was most commonly identified using case ascertainment tools, either in isolation [6, 42, 45, 56, 57] or in addition to clinical history and examination [3, 48, 51, 62]. Three studies [18, 25, 40] 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 [55] and this was cited by less than half (five out of twelve) of the studies [3, 6, 18, 40, 42]. With reference to the IASP grading system, the most common working hypothesis of neuropathic pain was 'probable' [3, 18, 40]. Three studies defined neuropathic pain using a mechanisms based classification, without specific reference to the IASP definition [48, 51, 62]. 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') [45].

3.2. Prevalence

3.2.1. Quality assessment of prevalence studies

Seven studies reported prevalence estimates. External validity of the studies was of moderate to high risk of bias (see Figure 2 for a summary and Supplementary Materials Table S4 for full details of quality assessment of the included studies). For all seven studies, internal validity was at lower risk of bias than external validity. Overall, five out of the seven studies were deemed to be of moderate risk of bias [3, 45, 48, 57, 62], where further research is likely to have an important impact on the confidence in the prevalence estimate and may also change the estimate [34]. Only two of the studies [6, 42] were considered to be of low risk of bias where further research is very unlikely to change confidence in the reported estimate [34].

3.2.2. Prevalence estimates

Prevalence estimates were derived from a total of 715 patients in the seven studies (Table 3). None of the studies reported confidence intervals for the prevalence estimates and all studies utilised small samples. Across the studies, the prevalence of neuropathic pain in LBLP varied from 19% to 80%. The prevalence of neuropathic pain in LBLP varied from 19% in a secondary care sample of LBLP patients who consulted an outpatients spine centre with either sciatica or referred leg pain, 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 was higher in populations of LBLP with sciatica [3, 57] compared to mixed populations of LBLP (i.e., sciatica and referred pain) (for example, Beith et al [6] and Morsø et al [42]).

Three studies reported prevalence using case ascertainment tools and also based on clinical diagnosis [3, 48, 62]. Two studies [48 62] reported that over 40% of LBLP patients in whom the pain was clinically diagnosed as neuropathic, presented without neuropathic pain characteristics. Attal et al [3] reported that 39% of LBLP patients with no neurological signs, reported neuropathic characteristics on Doleur Neuropathique en 4 (DN4) [10]. PainDETECT [24] was the most commonly used tool to derive an estimate of prevalence; three studies provided estimates for "possible" or "likely" neuropathic pain that ranged from 19% [42] and 23% [6] to 43% (for acute and subacute sciatica) and 46% (for chronic sciatica) [57]. For all three studies [6, 42, 57] the estimates for "uncertain" neuropathic pain were between 26% and 28%, showing less variation than the estimate of "possible" neuropathic pain.

3.3. Characteristics

3.3.1. Quality assessment of studies describing characteristics and prognosis

Ten of the included studies [6, 18, 25, 40, 42, 48, 51, 56, 57, 62] underwent quality assessment, by two independent reviewers, using the QUIPs tool. Figure 3 summarises the risk of bias for each of the domains of the QUIPS tool [29] (see Supplementary Materials Table S5 for full details of quality assessment of individual studies). Three of the included studies were considered to

be of low risk of bias and seven at moderate risk of bias. Two of the studies [48, 62] that reported characteristics of neuropathic pain in LBLP compared to non-neuropathic pain were assessed to be of low risk of bias. The remaining study that was also of low risk of bias was a case-control study [40].

3.3.1. Characteristics of neuropathic pain

The characteristics of neuropathic pain in LBLP are summarised in Table 4 and are described in more detail in the following section.

3.3.3.1 Pain characteristics

Pain intensity

Pain intensity was reported to be higher in LBLP patients with neuropathic pain compared to those patients without, in the two studies where neuropathic pain was defined by case ascertainment tools [42, 56]. Studies that classified neuropathic pain according to clinical assessment [25, 48, 62] showed less conclusive results; only Schafer et al [48] found any significant differences across diagnostic groups in pain intensity but still patients with "denervation" reported the same pain intensity as patients with "musculoskeletal" (non-neuropathic) LBLP.

Pain duration and pain location

As regards pain location, the results from four studies [6, 25, 48, 51] suggest it is likely that LBLP patients with neuropathic pain present with pain below the knee compared to those without, although it is also likely that LBLP patients with non-neuropathic pain may also

present with pain below the knee. Three studies with different sampling methods reported on pain duration in LBLP patients with neuropathic pain, and all described that the majority of patients reported long pain duration [18, 48, 51]. Schafer et al [48] reported a shorter pain duration for clinical presentations of LBLP with neuropathic pain compared to those without, however there was no significant difference between all four groups. Smart et al [51] reported the majority (77%) of patients with neuropathic pain had pain duration of under one year.

3.3.3.2 Clinical examination (including self-report sensory profile)

Two of the included studies [25, 40] reported the presence or absence of sensory signs associated with neuropathic pain, assessed either through quantitative sensory testing (QST) or through self-reported neuropathic characteristics [40]. Both studies used samples of patients with sciatica which they considered synonymous to neuropathic pain. In addition to reporting the results of QST, Freynhagen et al [25] also reported the clinical characteristics of patients clinically diagnosed with either sciatica or referred leg pain. When using QST as an extension of normal neurological examination, LBLP patients clinically diagnosed with non-neuropathic pain were as likely to have sensory changes as LBLP patients diagnosed with neuropathic pain [25]. Description of neurological examination findings, based on this one study [25], suggest that it is likely that LBLP patients with neuropathic pain have more sensory deficits and changes in straight leg raise, but that sensory changes may not be a specific indicator of neuropathic pain. The study by Mahn et al [40], based on self-reported neuropathic characteristics, reported that pain attacks were the most common

characteristic of patients with sciatica and thermal induced pain was the least common. In sciatica patients, based on cluster analysis of sensory profiles from self-reported neuropathic characteristics, five distinct subgroups of patients were reported, one subgroup described pain attacks and pressure induced pain. This subgroup was reported to be unique to patients with LBLP and not found in patients with other neuropathic clinical conditions such as painful diabetic neuropathy and post-herpetic neuralgia. Despite the studies by Mahn et al [40] and Freynhagen et al [25], not reporting on comparative patient populations with LBLP, they provide a useful description of the clinical characteristics and sensory profile of LBLP patients with neuropathic pain.

3.3.3.3 Back and leg pain-related disability

In all three studies [42, 48, 62], LBLP patients with neuropathic pain reported significantly higher levels of disability compared to patients with non-neuropathic pain. In one of the studies [42], LBLP patients with neuropathic pain reported a median Roland Morris Disability Questionnaire (RMDQ) score of 18 (inter quartile range (IQR) from 14 to 20) compared to those patients without neuropathic pain whose median RMDQ score was 10 (IQR 7 to 15), this difference was reported to be clinically important.

3.3.3.4. Psychological characteristics

Depression

Moderate to severe depressive symptoms were reported in 42% of LBLP patients with neuropathic pain, and neuropathic pain in LBLP was associated with more severe depressive symptoms than in those without neuropathic pain [56, 57]. Whether LBLP patients with neuropathic pain had more severe depression was not conclusive across all studies. In two studies with low risk of bias, Schafer et al [48], Walsh and Hall [62] reported no differences in depressive symptom severity across clinical presentations of LBLP with and without neuropathic pain. Both studies reported clinically "normal" levels of symptoms in their samples, as did Smart et al [51].

Anxiety

Three studies reported higher levels of anxiety in LBLP patients with neuropathic pain compared to non-neuropathic pain [48, 56, 57] and one study found no difference [62]. Although Schafer et al [48] reported a significant difference in anxiety levels between clinical presentations of LBLP with and without neuropathic pain, the level of anxiety in the whole cohort was low, and patients with neuropathic pain reported only mild anxiety levels.

Two other cohorts of patients [51, 62] reported comparable levels of anxiety to those reported by Schafer et al [48]. In both the studies by Smart et al [51], Walsh and Hall [62] normal to mild levels of anxiety were reported. From the studies reporting anxiety in LBLP patients with

neuropathic pain, there is some evidence that LBLP patients with neuropathic pain are more likely to report higher levels of anxiety compared to those without neuropathic pain.

Fear avoidance

Fear avoidance, measured using the Fear Avoidance Beliefs Questionnaire (FABQ) [61], was investigated in two studies [48, 62]. Significant differences across clinical presentations of LBLP with and without neuropathic pain were reported in the physical activity sub-scale but not in the work sub-scale, in one of the studies [62]. The study by Schafer et al [48] did not find any differences in fear avoidance across clinical presentations of LBLP with and without neuropathic pain.

3.3.3.5. Health related quality of life

Three studies, all with moderate risk of bias, reported on aspects of quality of life and general health. Tutoglu et al [56] used domains of the Short Form health survey (SF-36) [64] to report on quality of life. Morsø et al [42] used a self-report numerical rating scale (0-10) for general health, and one further study [40] reported on sleep using the medical outcome scale [30]. Morsø et al [42] found that general health in LBLP patients with neuropathic pain was worse than in those with non-neuropathic pain. Similar findings were reported by Tutoglu et al [56] who found that all seven dimensions of the SF-36 (physical function, physical role, emotional role, social function, mental health, energy/vitality and pain) were worse for LBLP patients with neuropathic pain compared to those without. Mahn et al [40] reported that sleep was optimal in 37% of LBLP patients with neuropathic pain, with these patients also

reporting sleep disturbance and somnolence. There was some consistent evidence that LBLP patients with neuropathic pain presented with poorer quality of life compared to those without neuropathic pain, however evidence for sleep in this patient population was limited.

3.3.3.6 Medication use

Two studies [25, 42], with moderate risk of bias, reported that LBLP patients with neuropathic pain use significantly more analgesia than LBLP patients with non-neuropathic pain. They are also more likely to use opioid medications compared to LBLP patients without neuropathic pain. Both patient groups report similar use of non-steroidal anti-inflammatory drugs [25]. Amongst these two studies there is consistent low level evidence that patients with neuropathic pain are managed with more analgesia than those with non-neuropathic pain. It is not clear from these studies whether medication use is a feature of neuropathic pain or a result of the sampling methods used, or whether the use of medication was associated with improved outcomes in LBLP patients with neuropathic pain.

3.4. Prognosis

Two studies reported longitudinal data [42, 48], one of which described overall prognosis (clinical course) [42]. Schafer et al [48] reported on patient outcomes following treatment patients were clinically assessed to have LBLP related to neuropathic pain, both with and without neuropathic characteristics (patients were classified into one of four groups,

neuropathic sensitisation, denervation, peripheral nerve sensitisation or 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 [48]: 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. Neither the study by Schafer et al [48] nor the one by Morsø et al [42] provided any evidence of prognostic factors of neuropathic pain in LBLP.

Morsø et al [42] 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 5). 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.

4. Discussion

This is the first systematic review to synthesise available published evidence about the prevalence, characteristics and prognosis of LBLP patients with neuropathic pain. Heterogeneity of the included studies prevented meta-analysis, but comparisons between

studies and settings were still possible in relation to study design, quality and strengths and weaknesses.

4.1. Prevalence

In this systematic review, prevalence estimates were extrapolated from data from seven studies that were based in either primary care or in clinical settings that patients could feasibly have accessed directly, and therefore the population samples were considered to be similar. Overall prevalence reported in this systematic review varied widely. This is not the first systematic review to report variation in prevalence estimates, variation is reported in reviews of neuropathic pain populations in the general population (irrespective of clinical condition) [59] and in populations seeking care for non-specific LBP [22, 35]. 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 all 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 [59]. In a study included in this review, Walsh and Hall [62] 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) they reported a prevalence of 42% (19 out of 45

patients) when using the DN4. The later study by Walsh and Hall [62] 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 [60]. Identification of LBLP subgroups on the basis of the presence or absence of neuropathic characteristics is supported by previous research of patients with LBLP and other neuropathic pain conditions such as painful diabetic neuropathy and post-herpetic neuralgia [5]. Whether different subgroups of LBLP patients with neuropathic pain have different characteristics is not clear from the results of this systematic review but it is an implication for the development of targeted treatments in this patient population. The variation in prevalence reported in this systematic review in part, reflects inconsistency in defining cases of neuropathic pain both in research and in clinical practice. 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 pain, but not all patients with sciatica have neuropathic type of 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.

4.2. Characteristics and prognosis

The included studies in this systematic review reported some consistent evidence for worse back and leg pain-related disability in LBLP patients with neuropathic pain. In part, this is consistent with the wider literature on neuropathic pain, patients with neuropathic pain

have been reported to have worse morbidity than those without. Patients with neuropathic pain in the general population, irrespective of clinical condition, have been reported to have poor quality of life [54]. Depression and anxiety symptoms were commonly reported in patients with uncontrollable neuropathic pain [17]. The results also mirror findings from studies of the broader population of patients with neuropathic pain in LBP, where disability [24, 46], quality of life [33], pain intensity [24, 47] depression and anxiety [24] are worse in patients with neuropathic pain.

Similarly, 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 two remaining studies [48, 62], assessed to be of low risk of bias, reported fewer differences in pain intensity, depression and anxiety between patients with and without neuropathic pain. Unlike the other included studies, these two used clinical assessment to identify cases of neuropathic pain in LBLP patients. Both [48, 62] however, had small samples across four groups and it may be argued they lacked the power to detect any differences in characteristics between groups. 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. Overall, it is not clear whether back and leg pain-related morbidity in patients with neuropathic pain is due to the use of different methods of defining and identifying cases of neuropathic pain or whether it is due to differences in study design and perhaps methodological quality.

Individual components from history taking (pain location) and neurological clinical examination were reported in a number of studies included in this review. In four of the studies [6, 25, 48, 51], 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 [25] 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 Attal et al [3] who reported that patients with neuropathic characteristics were more typical of sciatica but neuropathic characteristics were not restricted to patients clinically classified as having sciatica. Conversely, a subgroup of patients with a clinical diagnosis of sciatica have no features of neuropathic pain [40, 48, 62], 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.

It is physiologically feasible that underlying nociceptive stimuli causing LBLP, for example degeneration of an intervertebral disc, over time may involve microscopic nerve fibres [4]. 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 it is not known whether patients who initially present with neuropathic pain continue to have signs and symptoms of neuropathic pain over time. In this systematic review, there was inconclusive evidence, from three studies, that patients with neuropathic pain report longer pain duration.

Only one of the two identified studies with longitudinal data described prognosis in LBLP patients with neuropathic pain [42]. Neither study with longitudinal data reported whether LBLP patients with or without neuropathic pain at baseline, might change in terms of presence or absence of signs and symptoms of neuropathic pain over time. The study by Morsø et al [42] 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. It is not clear from their study [42] whether LBLP may change from a neuropathic state to non-neuropathic and vice versa, and they did not investigate prognostic factors associated with recovery from pain or disability in LBLP patients with neuropathic pain. Prognostic research offers the opportunity for clinicians and patients to understand what is going 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 [26]. It is not clear from this systematic review whether LBLP patients with neuropathic pain have more symptoms 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 [15].

4.3. Strengths and limitations

This review used a comprehensive systematic approach that was applied throughout the study. An exhaustive search strategy was developed and applied using six search engines. Additional searches and citation tracking were also executed, however some supporting

evidence may have been missed, for example, studies not published as full text. A further limitation was the inability to provide pooled estimates of prevalence and characteristics, because of heterogeneity between studies. An important strength of this review was the use of two quality assessment tools, one for prevalence studies and one for the studies on characteristics and prognosis.

4.4. Implications for research and clinical practice

This systematic review highlights the need for high quality research on the epidemiology of neuropathic pain in LBLP patients in clinical settings such as primary care, where the majority of LBLP patients consult and are treated. 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. Currently there is an absence of available evidence in this important patient group. The review also identified that there may be different subgroups of LBLP patients with or without neuropathic characteristics. 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.

4.5. Conclusions

This systematic review of LBLP patients with neuropathic pain, found a wide variation in reported prevalence estimates, 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 or without neuropathic pain is likely to inform decision making in clinical practice, it may also contribute to the timely delivery of targeted treatment interventions, such as specific medications, for this group of patients.

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Table and Figure Legends

Figure 1. Flow chart of systematic search and study selection (adapted from the PRISMA flow chart) [41]

Figure 2. Summary of quality assessment [34] (described as a proportion (%) of studies by risk of bias) of the seven included studies used to derive prevalence

Figure 3. Summary of quality assessment [29] (described as a proportion (%) of studies by risk of bias) of the ten included studies used to describe characteristics and prognosis

Table 1. Eligibility criteria for study selection, detailing an itemised description of the inclusion and exclusion criteria for this review

Table 2. Summary of all 12 studies included in the systematic review

Table 3. Studies providing prevalence estimates of neuropathic pain in low back-related leg pain, grouped by method of establishing neuropathic pain

Table 4. Studies describing characteristics of neuropathic pain in low back-related leg pain (LBLP)

Table 5. Study by Morsø et al [42] showing overall prognosis (using results obtained through personal communication with the author) of neuropathic pain in low back-related leg pain (n=145)

Table 1. Eligibility criteria for study selection, detailing an itemised description of the inclusion and exclusion criteria for this review.

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:
  o occupational settings
  o physiotherapy outpatients, general practice, osteopathic or chiropractic clinics
  o 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:
  o 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:
  o 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:
  o Settings where spinal surgery, spinal cord stimulation, caudal epidural or facet joint injections or spinal nerve root blocks were carried out

Table 2. Summary of all 12 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 [55]	Setting:
Attal et al. (2011)[3], 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)[6], UK	Cross-sectional	Mixed* LBLP	N=227 (NR)% M Age: NR	Yes	PainDETECT	Possible	Physiotherapy referrals in primary care and secondary care
Defrin et al. (2014)[18] 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	Case	Sciatica	Radicular pain‖:	Yes	Clinical history,	Not defined	Pain medicine,

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 [55]	Setting:
et al. (2008) [25], Germany	control	(chronic unilateral leg pain)	N = 15, 42% M Age: 54 (16) Pseudoradicular pain: N = 12, 44% M Age: 52 (16)		examination and imaging/ electrophysiology where indicated		neurology and neurosurgery setting
Mahn et al. (2011), [40], 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) [42], Denmark	Cross-sectional with follow up data	Mixed* LBLP > 3 months and <12 months	N=145 39% M Age: 50 (15)	Yes	PainDETECT	Possible	Outpatient spine centre in Secondary care
Ouédraogo et al. (2012) [45], Burkina Faso	Cross-sectional	Mixed* LBLP	N = 66 (NR)%M Age: NR	Yes	DN4	Not defined	Rheumatology, Neurology and Neurosurgery clinics
Schafer et al. (2011) [48], Germany	Cross-sectional follow up	Mixed* LBLP > 6 weeks and NRS	N=74 40% M Age: 48 (13)	Yes	LANSS and clinical assessment to	Not defined	MDT pain 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 [55]	Setting:
	data	>3/10 ‡			determine neural related leg pain classification		
Smart et al. (2012) [51], 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)
Tutoglu et al. (2015) [56] Turkey	Case control	Sciatica	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
Uher and Bob (2013), [57],	Cross-sectional	Sciatica	N=66 42% M Age: 58 (NR)	Yes	PainDETECT (Czech version)	Not defined	Neurology Inpatients

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 [55]	Setting:
Czech Republic							
Walsh and Hall (2009) [62], Ireland	Cross-sectional	Mixed* LBLP‡	N=45 49% M Age: 46 (11)	Yes	S-LANSS and clinical assessment to determine neuropathic related leg pain	Not defined	Back pain clinic

DN4, Doleur Neuropathique en 4 [10]. L4, L5, S1, lumbar spinal nerve roots. LANSS, Leeds Assessment of Neuropathic Symptoms and Signs [7]. LBLP, low back-related leg pain. M, male. MDT, multi-disciplinary team. MRI, magnetic resonance imaging. NR, not reported. NRS, numerical rating scale. PainDETECT, [24]. QTSFD, Quebec task force classification of spinal disorder. S-LANSS, Self-report version of the Leeds Assessment of Neuropathic Symptoms and Signs [8]. VAS, visual analogue scale.

* Mixed LBLP: heterogeneous samples of 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.

‡ 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.

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 [55]	Setting:
¶ Grouped as sciatica and neuropathic pain, sciatica and non-neuropathic pain and a control group.							

Table 3. Studies providing prevalence estimates of neuropathic pain in low back-related leg pain, grouped by method of establishing neuropathic pain.

Study	Case ascertainment tool used to derive neuropathic pain	Numerator used for calculation of prevalence	Prevalence of neuropathic pain (%)*
[3]	DN4	LBLP	49
		QTSFD† group 4	80
		QTSFD† group 3	39
		QTSFD† group 2	15
[45]	DN4	LBLP	61
[48]	LANSS	LBLP with LANSS ≥12 and clinical examination confirming neuropathic pain	26
		LBLP with clinical examination confirming neuropathic pain but with LANSS <12	47
[62]	S-LANSS	LBLP with S-LANSS ≥12 and clinical examination confirming neuropathic pain	33
		LBLP with clinical examination confirming neuropathic pain but with S-LANSS <12	40
[42]	PainDETECT	LBLP with "possible" neuropathic pain component	19
		LBLP with "uncertain" pain classification	26
[57]	PainDETECT	Acute and sub-acute sciatica with "possible" neuropathic pain component	43
		Acute and sub-acute sciatica with "uncertain" pain classification	28
		Chronic sciatica with "possible" neuropathic pain component	46
		Chronic sciatica with "uncertain" pain classification	27
[6]	PainDETECT	LBLP with "possible" neuropathic pain component	23
		LBLP with "uncertain" pain classification	27

DN4, Doleur Neuropathique en 4 [10]. LANSS, Leeds Assessment of Neuropathic Symptoms and Signs [7]. LBLP, Low back-related leg pain. PainDETECT, [24]. 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.

Table 4. Studies describing characteristics of neuropathic pain in low back-related leg pain (LBLP)

Characteristic associated with neuropathic pain	Study	Outcome measure used	LBLP patients with neuropathic pain	LBLP with non-neuropathic pain	Reported P
Pain intensity	[25]	NRS (unspecified whether for back or leg)	Mean 6.4 (SD 1.8)	Mean 5.3 (SD 2.3)	0.19
	[42]	NRS 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 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
	[48]	NRS (unspecified whether back or leg)	Neuropathic sensitisation mean 5.8 (SD 1.7); peripheral nerve sensitisation mean 5.3 (SD 1.7); denervation mean 4.6 (SD 1.5)	Mean 4.6 (SD 1.4)	0.031
	[56]	VAS (unspecified whether back or leg)	Mean 8.0 (SD 1.6)	Mean 6.6 (SD 3.4)	0.033
	[62]	VAS (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
Pain location	[6]	% reporting pain below the knee	79% of LBLP patients with possible neuropathic pain, 74% of LBLP with uncertain pain	57%	n/a
	[25]	% reporting pain in the leg	Radiating pain below the knee: in S1 dermatomal distribution 25%, in L5 dermatomal distribution 50%, to L4 17%,	Radiating pain to the gluteal region or thigh (but not below knee) 100%	n/a

Characteristic associated with neuropathic pain	Study	Outcome measure used	LBLP patients with neuropathic pain	LBLP with non-neuropathic pain	Reported P
			to L4 & L5 8%		
	[48]	% reporting pain below knee	Neuropathic sensitisation 80.0%, peripheral nerve sensitisation 88.9%, denervation 71.4%	73.7%	0.71
	[51]	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	[18] †	Years	With allodynia mean 5.7 (SD 5.6) Without allodynia mean 2.7 (SD 2.9)	n/a	n/a
	[48]	Current episode (months)	Neuropathic sensitisation mean 7.0 (SD 18.4); peripheral nerve sensitisation mean 6.0 (SD 12.5); denervation mean 7.3 (SD 11.3)	Mean 10.6 (SD 12.2)	0.76
	[51]	Current episode	0 to 12 weeks (34%), 4 to 12 months (43%), 1 year and over (23%)	n/a	n/a
Back and leg pain-related disability	[42]	RMDQ	Median 18, IQR 14 to 20	Median 10, IQR 7 to 15	0.000
	[48]	RMDQ	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
	[62]	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

Characteristic associated with neuropathic pain	Study	Outcome measure used	LBLP patients with neuropathic pain	LBLP with non-neuropathic pain	Reported P
Psychological characteristics (depression)	[40] †	PH9	None (23%), mild (35%), moderate (37%), severe (5%).	n/a	n/a
	[48]	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)	0.37
	[51]	HADS	Mean 7.0 (SD 4.4)	n/a	n/a
	[56]	BDI	Mean 20.9 (SD 12.4)	Mean 5.9 (SD 5.4)	<0.001
	[57]	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
	[62]	HADS	Neuropathic sensitisation mean 7 (SD 4); peripheral nerve sensitisation mean 8 (SD 4); denervation mean 5 (SD 3)	Mean 5 (SD 3)	0.12
Psychological characteristics (anxiety)	[48]	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
	[51]	HADS	Mean 7.5 (SD 4.4)	n/a	n/a
	[56]	BAI	Mean 10.2 (SD 10.8)	Mean 3.1 (SD 3.7)	<0.001
	[57]	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
	[62]	HADS	Neuropathic sensitisation mean 9 (SD 4); peripheral nerve sensitisation mean 10 (4); denervation mean 7 (SD 3)	Mean 7 (SD 2)	0.14

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)	[48]	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
	[62]	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
	[62]	FABQ - Work	Neuropathic sensitisation mean 22 (SD 11); peripheral nerve sensitisation mean 21 (SD 11); denervation mean 21 (SD 13)	Mean 22 (SD 13)	0.99
Health related quality of life	[42]	Self-rated general health (0-10)	Median 2, IQR 1 to 3	Median 3, IQR 2 to 4	0.001
	[56]	SF-36 physical function	Mean 44.3 (SD 26.3)	Mean 77.7 (SD 24.7)	<0.001
		SF-36 physical role	Mean 1.9 (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
		SF-36 general health	Mean 36.1 (SD 13.3)	Mean 40.8 (SD 10.9)	<0.001
Health related quality of life (sleep)	[40] †	Sleep (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
Other	[25]	Clinical examination	Positive neural tension tests (proportion	Positive straight leg raise	n/a

Characteristic associated with neuropathic pain	Study	Outcome measure used	LBLP patients with neuropathic pain	LBLP with non-neuropathic pain	Reported P
characteristics			of sample, 42%), positive straight leg raise (50%), reflex deficit (25%), sensory deficit (58%), motor deficit (25%)	(proportion of sample, 13%), sensory deficit (20%)	
	[40]	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

† Characteristics derived from case control studies and the reported associations are for LBLP patients with neuropathic pain only.
†† Sleep disturbance, somnolence and sleep adequacy are reported on a VAS of 0 to 100.
BAI, Beck anxiety inventory. BDI, Beck depression inventory. BDI-II, Beck depression inventory (Czech version). FABQ, Fear avoidance beliefs questionnaire. IQR, interquartile range. LBLP, low back-related leg pain. MOS, Medical outcome study. n/a, not applicable. 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.

Table 5. Study by Morsø et al [42] showing overall prognosis (using results obtained through personal communication with the author) 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 neuropathic and non-neuropathic pain patients (shown as reported P value)**		
	Baseline	3 months		12 months		Baseline	3 months		12 months		Baseline	3 months	12 months
	Median	Median	P	Median	P	Median	Median	P	Median	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
Leg and back pain 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
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

† 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

NRS, numerical rating scale. RMDQ, Roland Morris Disability Questionnaire

Figure 1. Flow chart of systematic search and study selection (adapted from the PRISMA flow chart) [41].

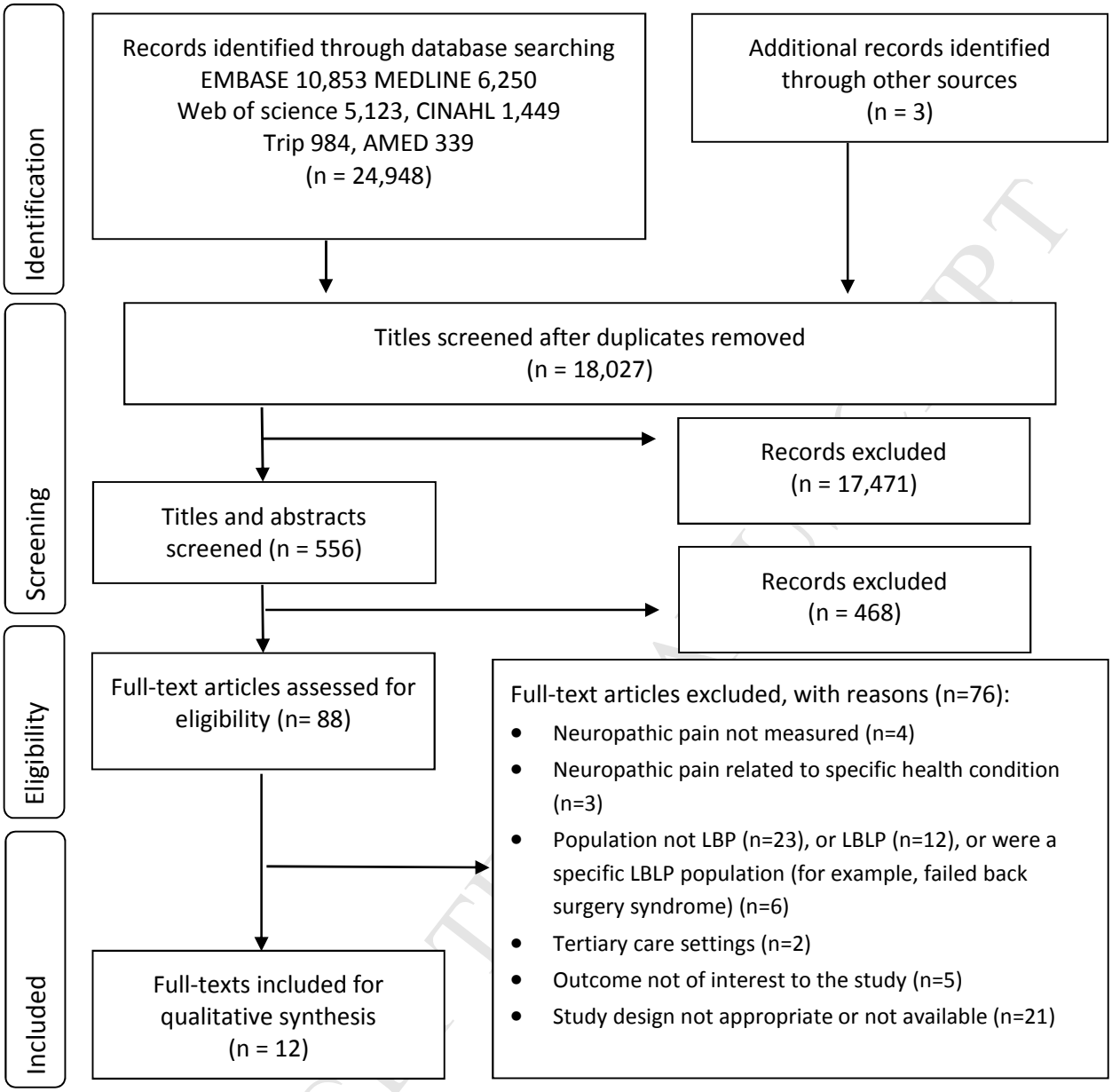


Figure 2. Summary of quality assessment [34] (described as a proportion (%) of studies by risk of bias) of the seven included studies used to derive prevalence.

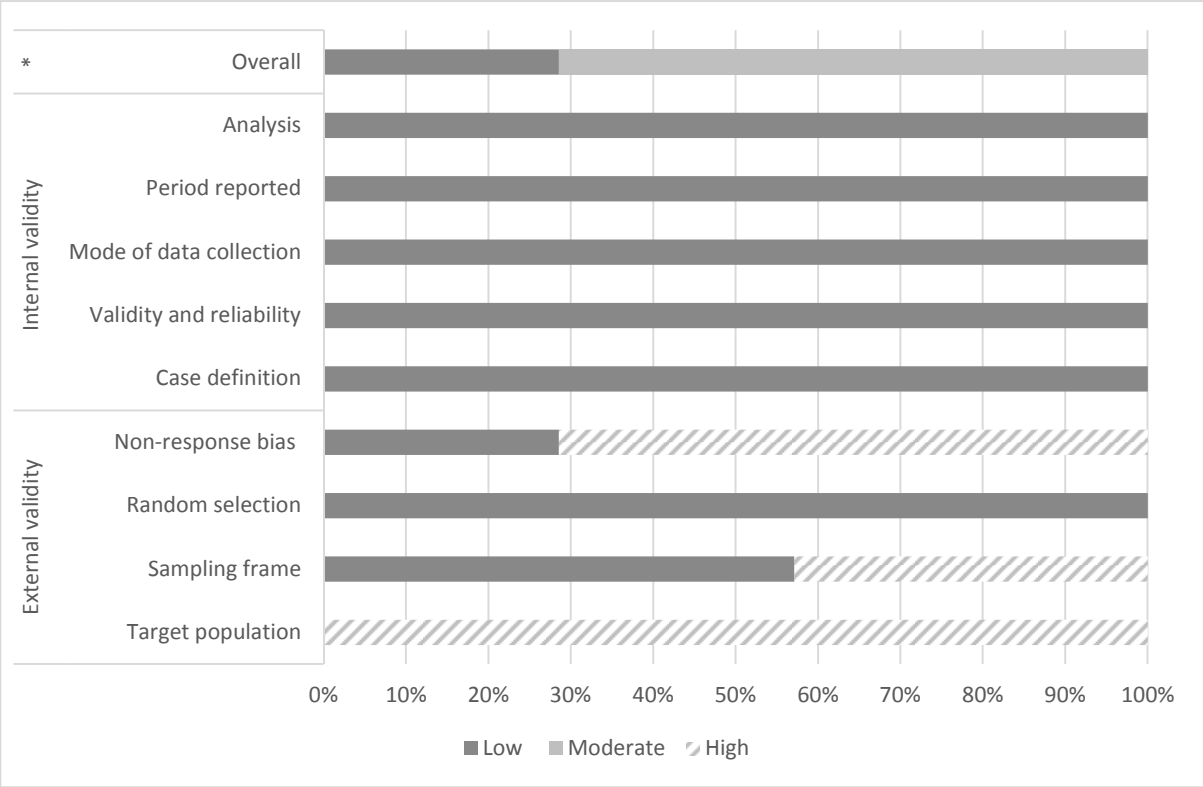
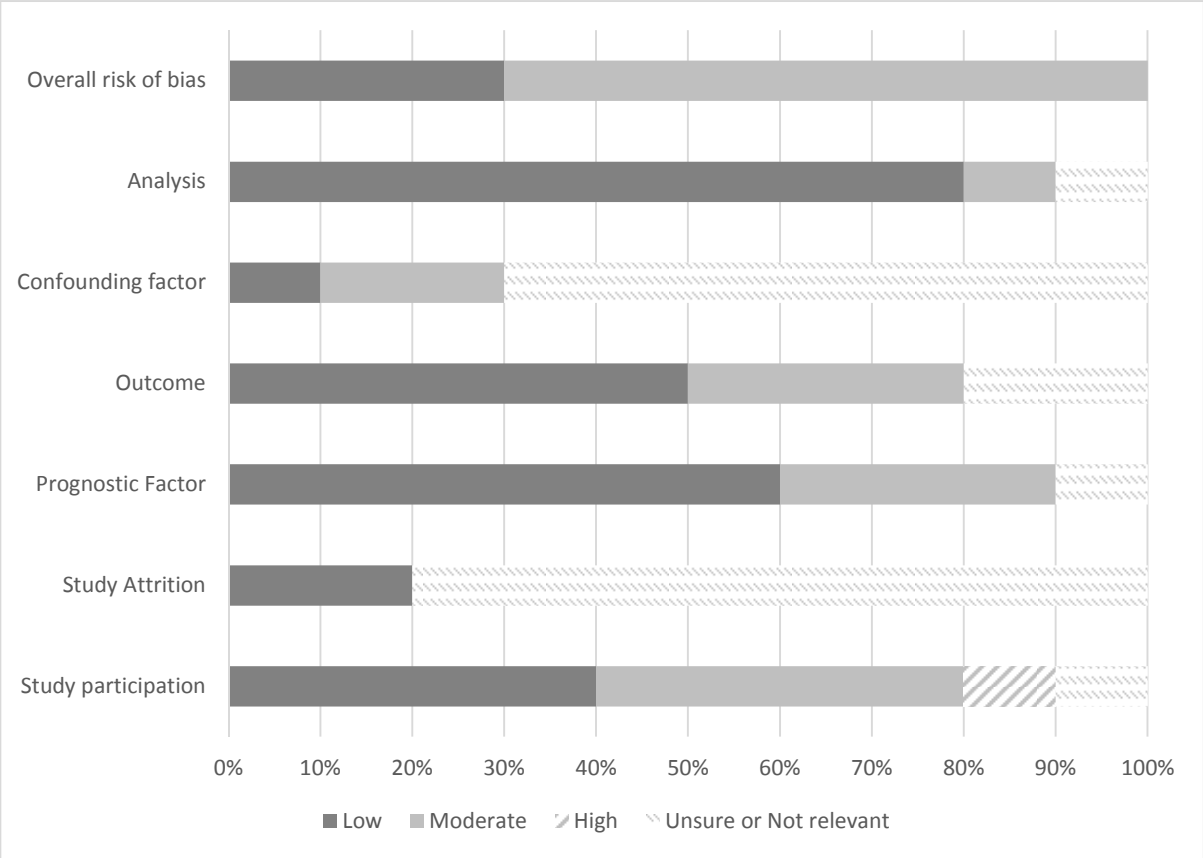


Figure 3. Summary of quality assessment [29] (described as a proportion (%) of studies by risk of bias) of the ten included studies used to describe characteristics and prognosis



Highlights

- 12 studies were included in the review
- Prevalence estimates of neuropathic pain in LBLP patients varied from 19% to 80%
- Consistent evidence for worse disability in LBLP patients with neuropathic pain vs those without
- Based on one study, prognosis was worse for LBLP patients with neuropathic pain
- No evidence found on characteristics associated with prognosis (prognostic factors)