Diagnostic utility of patient history, clinical examination and screening tool data to identify neuropathic pain in low back-related leg pain: protocol for a systematic review

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ABSTRACT

Introduction  Neuropathic low back-related leg pain (LBP) can be a challenge to healthcare providers to diagnose and treat. Accurate diagnosis of neuropathic pain is fundamental to ensure appropriate intervention is given. However, to date there is no gold standard to diagnose neuropathic LBP. Patient examination guidelines and screening tools have been developed and validated for the purpose of diagnosing neuropathic pain in LBP; however, there has been no systematic review conducted to compare the diagnostic validity of these methods. Therefore, this systematic review will investigate the diagnostic utility of patient history, clinical examination and screening tool data to identify neuropathic pain in LBP.

Methods and analysis  This protocol is informed and reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols. CINAHL, EMBASE, MEDLINE, Web of Science, Cochrane Library, AMED, Pedro, PubMed, key journals and grey literature will be searched rigorously to find diagnostic accuracy studies investigating patient examination data to identify neuropathic pain in LBP patients. Two independent reviewers will conduct the search, extract the data and assess risk of bias for included studies using the Quality Assessment of Diagnostic Accuracy Studies 2 tool. The overall quality of included studies will be evaluated using Grading of Recommendations, Assessment, Development and Evaluation guidelines. A meta-analysis will be conducted if deemed appropriate. Otherwise, a narrative synthesis will be conducted.

Ethics and dissemination  No research ethics is required for this systematic review since patient data will not be collected. This review will help to inform healthcare professionals and researchers on the most effective means in which to diagnose neuropathic pain in LBP. Results of this review will be submitted for publication in a peer-review journal and conference presentations.

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INTRODUCTION

Neuropathic pain is widely recognised as a pain syndrome which is both difficult to diagnose and treat.1 The International Association of the Study of Pain defines neuropathic pain as ‘pain that arises as a direct consequence of a lesion or diseases affecting the somatosensory nervous system’.2 People experiencing low back pain (LBP) with associated leg pain are among the most common subgroups to experience neuropathic pain.3 Low back-related leg pain (LBP) compared with LBP alone is associated with increased disability, pain and poorer quality of life.4 LBP is generally clinically diagnosed as sciatica (lumbar radicular) or referred pain (involving non-neural structures); sciatica is considered neuropathic in nature whereas referred pain is considered nociceptive.5 However, there is evidence to suggest the coexistence of both pain mechanisms in LBP,6 and evidence for sciatica presenting without neuropathic pain and referred pain presenting with neuropathic pain.7 In a recent systematic review

Strengths and limitations of this study

This will be the first systematic review to evaluate the diagnostic validity of patient history, objective examination and screening tool data to identify neuropathic pain in low back-related leg pain.

Studies will be obtained from a wide range of platforms including electronic databases, key journals and the grey literature.

This systematic review will be conducted according to The Cochrane Handbook for Diagnostic Test Accuracy studies.

Studies will be assessed for risk of bias using the Quality Assessment of Diagnostic Accuracy Studies 2 tool and the overall quality of evidence will be reported using the Grading of Recommendations Assessment, Development and Evaluation.

A limitation of this review is an acknowledged lack of an accepted reference standard for this type of diagnosis.
investigating the prevalence, characteristics and prognosis of neuropathic pain in LBLP in a primary care setting, Harrisson et al found that prevalence estimates of neuropathic pain in LBLP ranged from 19% to 80%. Nevertheless, the findings of this review must be observed with caution as the review itself presents with moderate risk of bias. A factor which may have contributed the large range of prevalence could be the difference in measuring neuropathic pain. Methods of measuring neuropathic pain in the included studies of Harrisson et al's review included: clinical history taking, screening tools and imaging.

Identification of patients with neuropathic pain in LBLP is essential as pharmaceutical intervention may improve patient outcomes. The National Institute for Health and Care Excellence (NICE) recommend medications such as amitriptyline, duloxetine, gabapentin or pregabalin during initial management of neuropathic pain. Further advice regarding medication prescription and onward referral to the wider multidisciplinary team are described for neuropathic-pain-specific syndromes. In comparison to the NICE guidelines for LBP and sciatica, pharmacological and further intervention recommendations differ, highlighting the importance of accurate identification of neuropathic pain to optimise evidence-based intervention.

There is no gold standard for diagnosing neuropathic pain. Consequently, expert opinion guidelines through a Delphi study and a variety of screening tools have been developed and used as reference standards in research studies. Neuropathic pain in LBLP research is most commonly identified using screening tools, including: PainDetect, Leeds Assessment of Neuropathic Symptoms and Signs and Douleur Neuropathique. Patient history and clinical examination data are also used but not as often. Studies have been conducted to investigate the diagnostic validity of screening tools and patient history/clinical examination data. However, these results have not been synthesised and evaluated. In order to ascertain the diagnostic validity of patient history, clinical examination and screening tool data to identify neuropathic pain in LBLP, a systematic review is required.

Objective
To evaluate the diagnostic utility of patient history, clinical examination and screening tool data in order to identify neuropathic pain in adults presenting with LBLP.

METHODS
A systematic review will be conducted according to this predefined protocol designed using The Cochrane Handbook for Diagnostic Test Accuracy studies and the Centre for Reviews and Dissemination (CRD, 2009). An initial scoping review of the literature informed the feasibility of the study objective being addressed. The protocol is reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis-Protocols (PRISMA-P) checklist. Protocol amendments will be recorded and included in dissemination.

Patient and public involvement
Information from patients and the public has informed the conception and requirement for this review as part of an existing programme of research that is centred on lumbar spinal surgery for back-related leg pain and patient outcome.

Eligibility criteria
Inclusion criteria
Eligibility criteria were informed using the Sample, Phenomenon of Interest, Design, Evaluation, Research Type (SPIDER) guidelines.

(S) Sample: adult patients (age >18 years) with LBLP. (PI) Phenomenon of Interest: neuropathic pain in LBLP. (D) Design: any study design using primary diagnostic accuracy data. (E) Evaluation: any study reporting on the diagnostic validity of patient history (includes any component of a patient history, for example, pain location, history of nerve injury, pain description and so on), clinical examination (includes any component of a physical clinical examination, for example, neurodynamic testing, quantitative sensory testing, movement provocation tests and so on), screening tool data to identify neuropathic pain in LBLP. The use of imaging as a clinical indicator of neuropathic pain in LBLP will not be considered in this review as it is well established that structural abnormalities are not directly correlated with symptom presentation.

Exclusion criteria
Studies not written in English will be excluded. Studies that did not compare patient history and/or clinical examination and/or screening tools against a reference standard (eg, clinical expert opinion) will also be excluded.

Information sources
Each database will be searched from inception to 31 July 2019. The search strategy will be specific to each database. There will be no geographical restrictions. The databases that will be searched are CINAHL, EMBASE, MEDLINE, Web of Science, Cochrane Library, AMED, Pedro and PubMed. Hand searching of key journals will include: Musculoskeletal Science and Practice, PAIN, European Journal of Pain, The Journal of Pain and The Clinical Journal of Pain. The Cochrane Back Review Group and the reference lists of all included studies will be reviewed for further relevant studies. Grey Literature will be searched.
Box 1  Example of Medline OvidSP search strategy 1948–July 2019

1. exp “Sensitivity and Specificity”/ or Diagnostic accuracy.mp.
2. diagnostic utility.mp.
3. exp “Reproducibility of Results”/ or exp “Sensitivity and Specificity”/ or diagnostic reliability.mp.
4. 1 or 2 or 3
5. patient history.mp.
6. patient interview.mp.
7. subjective history.mp.
8. subjective examination.mp.
9. physical examination.mp. or exp Physical Examination/
10. physical testing.mp.
11. objective examination.mp.
12. objective history.mp.
13. clinical examination.mp.
14. clinical testing.mp.
15. case ascertainment tool$.mp.
16. screening tool$.mp.
17. questionnaire$ or exp “Surveys and Questionnaires”/
18. 5 or 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17
19. 4 and 18
20. neuropathic pain.mp. or exp Neuropalgia/
21. radicular.mp. or exp Radiculopathy/ or exp Intervertebral Disc Displacement/ or exp Spinal Nerve Roots/
22. exp Sciatic Neuropathy/ or exp Sciatic Nerve/ or sciatic$.mp.
23. 20 or 21 or 22
24. 19 and 23
25. low back pain.mp. or exp Back Pain/ or exp Low Back Pain/
26. low back related leg pain.mp. or exp Sciatica/
27. 25 or 26
28. 24 and 27

via the British National bibliography for report literature, OpenGrey and EThOS.

Search strategy

The search strategy was developed by JM in discussion with the supervisory team and a specialist librarian. The search strategy will be specific to each database. The key terms used for the search will include diagnostic validity, patient history, clinical examination, screening tool, neuropathic pain and LBLP. For all key terms, a list of synonyms and truncations will be used within the search. See example in box 1.

Study records

Data management

Endnote Version X8 (Clarivate Analytics) software programme will be used to manage citations, references and bibliographies. EndNote will allow for duplicates to be identified and removed as well as storing of abstracts and full texts.

Selection process

Two review authors (JM, TN) will perform independent searches. Stage 1 of the selection process will involve screening of titles and abstracts using the eligibility criteria allowing for sub-categorisation into included/excluded/unsure groups. Stage 2 will involve retrieval of the full text of potentially relevant studies which will then be independently assessed by each reviewer (JM, TN). Studies will be included when both reviewers have assessed the full text for eligibility against the eligibility criteria. Disagreements will preferably be resolved through discussions or, if required by a third author (AR). There will not be a binding to trial authors, journals or institutions. The kappa statistic will be used to assess agreement between review authors at title/abstract screening stage and full-text screening stage.

Data collection process

Two review authors (JM, TN) will extract data independently using a customised data extraction form developed using The Cochrane Handbook for Diagnostic Test Accuracy studies. Initial piloting of the data extraction form will ensure all relevant information is collected. Disagreements will be resolved by consensus or, if required, by the third reviewer (AR), and the third reviewer will also independently check the data to ensure clarity and consistency. Study authors will be contacted via email,2,5 where required, in order to retrieve omitted or clarify study findings.

Data items

Data extracted will include study title, author and publication date, study design, participant characteristics (eg, age, gender, comorbidities), index test (which will be a test of diagnostic accuracy, specifically a component of patient history or clinical examination or a screening tool), comparator test, reference standard and data regarding the diagnostic validity of tests. Where data are available diagnostic accuracy data will be inputted into 2×2 contingency tables. The scoping review informed the feasibility of data being available. The key data of interest will be the diagnostic validity data and these values include sensitivity, specificity, PVs and LR.

Risk of bias in individual studies

Risk of bias of included studies will be assessed independently by the two reviewers (JM, TN) using the QUADAS-2 tool.29 QUADAS-2 is developed from the original QUADAS tool and is recommended to assess the risk of bias of primary diagnostic accuracy studies.29 QUADAS-2 consists of four domains with questions related to patient selection, index test, reference standard and flow and timing. Risk of bias for individual items is judged as ‘high’, ‘low’ or ‘unclear’ and a subsequent summary judgement of ‘at risk or low risk’ will be obtained for each study overall.29 Any disagreements between the two reviewers will be discussed in a consensus meeting. The third reviewer (AR) will be consulted where necessary. Cohen’s k will be used to assess agreement between the two reviewers.

Summary measures

Sensitivity, specificity, PV and LR will be presented as summary measures. In cases where only raw data are used, summary measures will be presented as meta-measures.
presented, the sensitivity, specificity, PVs and LR will be calculated according to the formulae of Akobeng. Summary measures will include details regarding level of accuracy of sensitivity and specificity, discriminatory properties of the test and strength of agreement in reliability.33

**Data synthesis**

Heterogeneity will be explored to evaluate if the studies are suitable for a meta-analysis. Study design, population, comparable diagnostic data and reference standard will be considered for clinical comparison.34 Following evaluation of scoping searches of the current available literature, pooling of data may not be possible due to heterogeneity within study design, population and reference standard. However, a meta-analysis will not be ruled out until data are assessed and, if deemed appropriate, a meta-analysis will be conducted. The narrative synthesis will be conducted in line with previously recommended guidance for a narrative synthesis in systematic reviews.35 The narrative synthesis will consist of three sections: developing a preliminary synthesis of findings of included studies, exploring relationships in the data and assessing the robustness of the synthesis.35 Preliminary synthesis of findings will be conducted with a short textual description of each included study. Exploring data relationships will be facilitated through thematic analysis to identify any common themes/trends within the included studies. The robustness of the data of included studies will be contextualised using Grading of Recommendations, Assessment, Development and Evaluation (GRADE) and the QUADAS-2 in a narrative format. Synthesis will bring together measures of diagnostic validity for data regarding patient history, clinical examination and screening tools. Within the narrative synthesis, reasons for data heterogeneity will be explored by considering study design, population, comparable diagnostic data and the reference standard.

**CONFIDENCE IN CUMULATIVE EVIDENCE**

The strength of the overall body of evidence will be assessed using the Grading of Recommendations, Assessment, Development and Evaluation guidelines (GRADE). GRADE will be used as recommended for diagnostic accuracy test studies.36 The GRADE approach begins by assigning a starting level of quality to findings, both cross sectional and cohort studies are considered ‘high quality’ whereas other quantitative study types are considered ‘low quality.’36 Subsequently, five factors are considered that can lead to a downgrading/or upgrading of the GRADE ranking; these include risk of bias, inconsistency of evidence, indirectness of evidence, imprecision of results and publication bias.36

**CLINICAL IMPLICATIONS**

Accurate diagnosis of neuropathic pain in LBLP is important as this will help to ensure precision management by healthcare professionals regarding the most appropriate intervention. Notwithstanding the range of approaches, including patient history, clinical examination and screening tools suggested to identify neuropathic LBLP, there is a lack of consensus regarding the most valid diagnostic method. This systematic review will collate data regarding the diagnostic validity of various means of identifying neuropathic pain in LBLP, to highlight the method which is superior. In doing so, health professionals will be made aware of the most valid method to use within clinical practice. This will enable timely and effective management of patients with neuropathic pain in LBLP.

Potential limitations of this review arise from our acknowledged lack of an accepted reference standard for this type of diagnosis, and therefore data on diagnostic accuracy might be limited. If the study’s findings do not permit for the research question to be answered (eg, due to heterogeneity among the current literature) then clear priorities for further research will be suggested following data synthesis in order to address this research question appropriately.

**ETHICS AND DISSEMINATION**

There will be no research ethics required for this systematic review due to no patient data being collected. This review will help to inform healthcare professionals and researchers on the most effective means in which to diagnose neuropathic pain in LBLP. Results of this review will be disseminated in a peer-review journal and relevant conferences.

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**Contributors** All authors devised the focus of the systematic review. JM is the MRes student, AR is the lead supervisor, NH and DF are co-supervisors and TN is the second reviewer. JM drafted the initial protocol manuscript with lead and co-supervisors providing guidance on methodological decisions and proposed analyses. All authors have contributed subject-specific expertise. All authors will contribute to data interpretation, conclusions and dissemination. All reviewers have read, contributed to, and agreed the final manuscript. AR is the guarantor of the review.

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REFERENCES
1. Freynhagen R, Bennett MI. Diagnosis and management of neuropathic pain. BMJ 2009;339:3002.
2. Treede R-D, Jensen TS, Campbell N, et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. Neurology 2008;70:1630–5.
3. Berger A, Sadosky A, Dukes E, et al. Clinical characteristics and patterns of healthcare utilization in patients with painful neuropathic disorders in UK general practice: a retrospective cohort study. BMC Neurology 2012;12:8.
4. Konstantinou K, Hider SL, Jordan JL, et al. The impact of low back-related leg pain on outcomes as compared with low back pain alone: a systematic review of the literature. Clin J Pain 2013;29:644–54.
5. Harrison SA, Stynes S, Dunn KM, et al. 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. J Pain 2017;18:1295–312.
6. Freynhagen R, Rolke R, Baron R, et al. Pseudoradicular and radicular low-back pain—a disease continuum rather than different entities? answers from quantitative sensory testing. Pain 2008;135:65–74.
7. Mahn F, Hüllemann P, Gockel U, et al. Sensory symptom profiles and co-morbidity in painful radiculopathy. PLoS One 2011;6:e18018.
8. van Hecke O, Austin SK, Khan RA, et al. Neuropathic pain in the general population: a systematic review of epidemiological studies. Pain 2014;155:854–62.
9. Beith ID, Kemp A, Kenyon J, et al. Identifying neuropathic back and leg pain: a cross-sectional study. Pain 2011;152:1511–6.
10. Ouedraogo D-D, Nonguierma V, Napon C, et al. Prevalence of neuropathic pain among black African patients suffering from common low back pain. Rheumatol Int 2012;32:2149–53.
11. Defrin R, Devor M, Brill S, et al. Tactile allodynia in patients with lumbar radicular pain (sciatica). Pain 2014;155:2551–9.
12. National Institute for Health and Care Excellence. Neuropathic pain – pharmacological management (NICE Guideline NG59). 2013. Available: https://www.nice.org.uk/guidance/cg172 [Accessed 10 May 2019].
13. National Institute for Health and Care Excellence. Low back pain and sciatica in over 16s: assessment and management (NICE guideline 33). 2016. Available: https://www.nice.org.uk/guidance/ng99 [Accessed 10 May 2019].
14. Smith BH, Torrance N, Bennett MI, et al. Health and quality of life associated with chronic pain of predominantly neuropathic origin in the community. Clin J Pain 2007;23:143–9.
15. Smart KM, Blake C, Staines A, et al. The Discriminative Validity of “Non nociceptive,” “Peripheral Neuropathic,” and “Central Sensitization” as Mechanisms-based Classifications of Musculoskeletal Pain. Clin J Pain 2011;27:655–63.
16. Walsh J, Hall T. Classification of low back-related leg pain: do subgroups differ in disability and psychosocial factors? J Manipulative Physiotherapy 2009;27:118–23.
17. Freynhagen R, Baron R, Gockel U, et al. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. Curr Med Res Opin 2006;22:1911–20.
18. Timmerman H, Steegers MAH, Huygen FJPM, et al. Investigating the validity of the DN4 in a consecutive population of patients with chronic pain. PLoS One 2017;12:e0187961.
19. Urban LM, MacNeil BJ. Diagnostic accuracy of the Slump test for identifying neuropathic pain in the lower limb. J Orthop Sports Phys Ther 2015;45:596–603.
20. Bossoyt P, Davenport C, Deeks J, et al. Chapter 11: Interpreting results and drawing conclusions. In: Cochrane Handbook for systematic reviews of diagnostic test accuracy version 0.9. The Cochrane Collaboration, 2013.
21. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015;349.
22. Cooke A, Smith D, Booth A, et al. Beyond PICO: the spider tool for qualitative evidence synthesis. Qual Health Res 2012;22:1435–43.
23. Kalichman L, Kim DH, Li L, et al. Computed tomography–evaluated features of spinal degeneration: prevalence, intercorrelation, and association with self-reported low back pain. Spine J 2010;10:200–8.
24. Leeflang MMG, Deeks JJ, Takwoingi Y, et al. Cochrane diagnostic test accuracy reviews. Syst Rev 2013;2:82.
25. van Tulder M, Furlan A, Bombardier C, et al. Updated method guidelines for systematic reviews in the Cochrane collaboration back review group. Spine 2003;28:1290–9.
26. Higgins J, Green S. Cochrane Handbook for systematic reviews of interventions. The Cochrane Collaboration, 2011.
27. Young T, Hopewell S. Methods for obtaining unpublished data. Cochrane Database Syst Rev 2011;MR00027.
28. Whiting PF, Davenport C, Jameson C, et al. How well do health professionals interpret diagnostic information? A systematic review. BMJ Open 2015;5:e008155.
29. Whiting PF, Rutjes AW, Westwood ME. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011;155:529–36.
30. Akobeng AK. Understanding diagnostic tests 1: sensitivity, specificity and predictive values. Acta Paediatr 2007;96:338–41.
31. Schneiders AG, Sullivan SJ, Hendrick PA, et al. The ability of clinical tests to diagnose stress fractures: a systematic review and meta-analysis. J Orthop Sports Phys Ther 2012;42:760–71.
32. Jaeschke R, Guyatt G, Sackett DL. Users’ guides to the medical literature. III. How to use an article about a diagnostic test. A. are the results of the study valid? Evidence-based medicine Working group. JAMA 1994;271:389–91.
33. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159–74.
34. Lijmer JG, Bossuyt PMM, Heisterkamp SH. Exploring sources of heterogeneity in systematic reviews of diagnostic tests. Stat Med 2002;21:1525–37.
35. Popay J, Roberts H, Sowden A, et al. Guidance on the conduct of narrative synthesis in systematic reviews: a product from the ESRC methods programme. Lancaster, UK: Lancaster University, 2006.
36. Schünemann HJ, Guyatt G, Oxman A, eds. The GRADE approach for diagnostic tests and strategies. GRADE handbook for grading quality of evidence and strength of recommendations. The GRADE working group, 2013.