BMJ Open 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 (LBLEP) 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 LBLEP. Patient examination guidelines and screening tools have been developed and validated for the purpose of diagnosing neuropathic pain in LBLEP; 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 LBLEP.

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 LBLEP 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 LBLEP. 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

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.

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 (LBLEP) compared with LBP alone is associated with increased disability, pain and poorer quality of life.⁴ LBLEP 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 LBLEP,⁶ and evidence for sciatica presenting without neuropathic pain and referred pain presenting with neuropathic pain.⁷ In a recent systematic review

investigating the prevalence, characteristics and prognosis of neuropathic pain in LBLP in a primary care setting, Harrisson *et al*⁶ 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.⁸ Methods of measuring neuropathic pain in the included studies of Harrisson *et al*'s review⁵ included: clinical history taking,^{6,7} screening tools^{9,10} and imaging.^{6,11}

Identification of patients with neuropathic pain in LBLP is essential as pharmaceutical intervention may improve patient outcomes.⁵ The National Institute for Health and Care Excellence (NICE)¹² 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,¹³ 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.¹⁴ Consequently, expert opinion guidelines¹⁵ through a Delphi study and a variety of screening tools have been developed and used as reference standards in research studies.⁵ Neuropathic pain in LBLP research is most commonly identified using screening tools, including: PainDetect,⁹ Leeds Assessment of Neuropathic Symptoms and Signs¹⁶ and Douleur Neuropathique 4.¹⁰ Patient history and clinical examination data are also used but not as often.⁶ Studies have been conducted to investigate the diagnostic validity of screening tools^{17,18} and patient history/clinical examination data.^{15,19} 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).²⁰ 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.²¹ 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.²²

(S) Sample: adult patients (age >18 years) with LBLP.

(PI) Phenomenon of Interest: neuropathic pain in LBLP.

(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.²³

(D) Design: any study design using primary diagnostic accuracy data. However, optimal study design would be cross-sectional studies.²⁴ Data including specificity, sensitivity, likelihood ratios (LRs) and predictive values (PVs) or presenting the raw data needed for calculation of these values.

(R) Research type: quantitative.

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\$.mp. 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 Neuralgia/
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.²⁵ 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 blinding 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.²⁶

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.²⁰ 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,²⁷ 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.²⁸ 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.²⁶

Summary measures

Sensitivity, specificity, PV and LR will be presented as summary measures. In cases where only raw data are

presented, the sensitivity, specificity, PVs and LR will be calculated according to the formulae of Akobeng.³⁰ Summary measures will include details regarding level of accuracy of sensitivity and specificity,³¹ discriminatory properties of the test³² 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. If a meta-analysis is not possible, a narrative synthesis 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 a MRes student, AR is the lead supervisor, NH and DF are cosupervisors and TN is the second reviewer. JM drafted the initial protocol manuscript with lead and cosupervisors 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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