Current Evidence for Diagnosis of Common Conditions

Causing Low Back Pain: Systematic Review and

Standardized Terminology Recommendations

FROM: J Manipulative Physiol Ther. 2019 (Nov); 42 (9): 651–664 ~ FULL TEXT

 OPEN ACCESS

Robert D. Vining, DC, DHSc • Zacariah K. Shannon, DC, MS

Amy L. Minkalis, DC, MS • Elissa J. Twist, DC, MS

Palmer Center for Chiropractic Research,

Palmer College of Chiropractic,

Davenport, Iowa.

 Thanks to JMPT for permission to reproduce this Open Access article!

OBJECTIVE: The purpose of this systematic review is to evaluate and summarize current evidence for diagnosis of common conditions causing low back pain and to propose standardized terminology use.

METHODS: A systematic review of the scientific literature was conducted from inception through December 2018. Electronic databases searched included PubMed, MEDLINE, CINAHL, Cochrane, and Index to Chiropractic Literature. Methodological quality was assessed with the Scottish Intercollegiate Guidelines Network checklists.

RESULTS: Of the 3,995 articles screened, 36 (8 systematic reviews and 28 individual studies) met final eligibility criteria. Diagnostic criteria for identifying likely discogenic, sacroiliac joint, and zygapophyseal (facet) joint pain are supported by clinical studies using injection-confirmed tissue provocation or anesthetic procedures. Diagnostic criteria for myofascial pain, sensitization (central and peripheral), and radicular pain are supported by expert consensus-level evidence. Criteria for radiculopathy and neurogenic claudication are supported by studies using combined expert-level consensus and imaging findings.

CONCLUSION: The absence of high-quality, objective, gold-standard diagnostic methods limits the accuracy of current evidence-based criteria and results in few high-quality studies with a low risk of bias in patient selection and reference standard diagnosis. These limitations suggest practitioners should use evidence-based criteria to inform working diagnoses rather than definitive diagnoses for low back pain. To avoid the unnecessary complexity and confusion created by multiple overlapping and nonspecific terms, adopting International Association for the Study of Pain terminology and definitions is recommended.

KEYWORDS: Diagnosis; Evidence-Based Practice; Low Back Pain; Systematic Review

From the FULL TEXT Article:

INTRODUCTION

Low back pain (LBP) is a substantial societal problem owing to high prevalence and the many problems associated with cost, chronicity, and disability. [1–3] Despite an intensive research focus on LBP, definitive diagnostic methods are largely unavailable and standard terminology is not yet broadly adopted,4 leading researchers and practitioners to classify most LBP as nonspecific. [2]

Nonspecific LBP represents a heterogenous group of conditions, which may respond differently to available interventions. Some evidence suggests that treatments based on subgroupings of patients with LBP may lead to more effective condition-tailored care. [5, 6] The lack of standard diagnostic methods for determining a conclusive diagnosis is due in part to many challenges with definitively confirming symptom sources and the co-occurrence of psychological and social factors that contribute to a person’s lived experience. [7, 8] Although identifying symptom sources is difficult in many cases, it is necessary to differentiate benign from ominous conditions and to meaningfully inform management approaches. [9–11]

Disparate diagnostic terminology creates potential confusion among both clinicians and researchers. For example, some clinical studies focused on sciatica, radiculopathy, or radicular pain instead report they are focused on discogenic pain. [12, 13] However, discogenic pain is defined as pain arising from the intervertebral disc, independent of nerve root involvement. [14] Spinal stenosis, a radiological finding describing a narrowed space, is a term synonymously used for the clinical syndrome of neurogenic claudication. [15] However, spinal stenosis is an anatomical characteristic that may not be associated with symptoms. [16]

To address some of the diagnostic challenges for LBP, an evidence-based diagnostic classification system was published in 2013 [17]; it defined diagnostic categories for neuromusculoskeletal LBP and reported evidence-based criteria supporting a variety of common diagnoses. A novel and practical diagnostic checklist and corresponding exam was also proposed to help practitioners interpret examination evidence to inform evidence-based working diagnoses. However, this classification system did not involve a systematic review of the literature or propose standardized terminology. Furthermore, evidence evolves over time, requiring periodic reevaluation to remain current.

An evidence-based working diagnosis using standardized terminology is needed to systematically explain the most likely biological processes contributing to LBP and to aid communication among providers, payers, and patients. The purpose of this study is to review current diagnostic evidence for office-based (ie, performed in office through examination, evaluating historical characteristics, or questionnaires) evaluation of common neuromusculoskeletal conditions causing LBP and to evaluate the quality and type of evidence of individual studies and systematic reviews focused on this topic. We provide recommendations for terminology use among clinicians and researchers. This systematic review will inform other studies that will offer a pragmatic office-based exam and diagnostic checklist, key aspects of efficient conduct of the exam, practical considerations for determining the relative strength of working diagnoses, and an evidence-based chiropractic treatment decision aid for managing LBP. [18, 19]

METHODS

This systematic review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and was registered with the International Prospective Register of Systematic Reviews (CRD42018099106). [20]

 Data Sources

A study team member (A.M.) with the assistance of a research librarian conducted an initial broad electronic search of literature in the databases PubMed, MEDLINE, CINAHL, Cochrane, and Index to Chiropractic Literature. The search dates were 2010 to November 2017. Based on the information gathered during the initial search, the authors conducted detailed searches of the same databases with search dates from inception to May 2018. Subsequently, searches were updated through December 31, 2018. Reference lists of articles meeting eligibility criteria were hand-searched, as were author-known articles included in the previous classification system. [17] Clinicaltrials.gov and the World Health Organization clinic trials registry databases were searched to identify relevant unpublished literature. [21] Search terms for each diagnosis addressed in this review are available as Appendix A.

 Inclusion/Exclusion Criteria

Articles were included if they were systematic reviews, meta-analyses, or individual studies including human participants focused on evaluating office-based exams or other diagnostic criteria for a specific diagnosis of neuromusculoskeletal LBP and published in English language peer-reviewed journals. Commentaries, narrative reviews, editorials, letters, conference abstracts, case reports/series, guidelines, inter-rater or testeretest reliability studies, and language validation studies were excluded.

 Study Selection

Figure 1

Two authors (E.T., Z.S.) independently reviewed titles, abstracts, and full-text articles against predetermined inclusion/exclusion criteria. Included systematic reviews and individual studies focused on diagnoses describing conditions arising from nociceptive signaling within the intervertebral disc, zygapophyseal (facet) joint(s), sacroiliac (SI) joint(s), and myofascial tissues, and neuropathic pain processes including radiculopathy, radicular pain, neurogenic claudication, and peripheral entrapment (piriformis and thoracolumbar [Maigne’s] syndrome). Central and peripheral sensitization were also included. Figure 1 visually displays the major neuromusculoskeletal diagnostic categories and subcategories included in this review.

 Quality Assessment and Data Extraction

Two authors (E.T., Z.S.) independently assessed article quality using methodology checklists developed by the Scottish Intercollegiate Guidelines Network (SIGN) (https://www.sign.ac.uk/checklists-and-notes.html). Because the SIGN methodology checklists are tailored to study design, methodology checklist 1 was used for systematic reviews and meta-analyses. Systematic reviews were assigned quality ratings based on 12 internal validity question scores. Articles were classified as high quality if the score was 10 or higher, acceptable quality for scores of 6 to 9, low quality for scores less than 6, or unacceptable quality if the research question and inclusion/exclusion criteria were not defined or a comprehensive literature search was not performed. Unacceptable quality systematic reviews were rejected. Individual studies that were not included within a systematic review were rated as high, low, or unclear for 4 risk-of-bias domains (patient selection, index test, reference standard, flow and timing) and 3 applicability domains (patient selection, index test, reference standard), using the SIGN methodology checklist 5 for studies of diagnostic accuracy. Disagreement of article quality was resolved by a third reviewer (A.M.) who independently assessed the article and generated a majority score. Data reporting key elements of all included studies (study design, performance statistics, study population, etc.) were abstracted independently by 3 authors (R.V., Z.S., A.M.). Each author verified each other’s work. Disagreement was resolved through consensus discussion among authors.

RESULTS

Figure 2

The initial search revealed 3,781 articles. A second updated search through December 2018 reveled an additional 45 articles. Hand searching revealed 169 additional articles, resulting in a total of 3,995. When 1,658 duplicates were removed, 2,337 articles remained for title and abstract review. After title and abstract review, 157 articles remained for full-text review. Twenty-five articles were excluded because they were evaluated in included systematic reviews (Appendix B). Thirty-six articles (8 systematic reviews and 28 individual studies) met final eligibility criteria. Of the 304 trial results displayed from search terms in both clinical trial registries (clinicaltrials.gov and World Health Organization), 2 studies were identified as potentially eligible with unpublished results. No response was received from requests for more information regarding these 2 trials. The search process is summarized in Figure 2.

Table 1

Table 1 [13, 15, 22–29] displays the systematic reviews included in this review, including the diagnostic foci and quality ratings. Ten reviews met initial eligibility criteria; 2 were deemed unacceptable quality, leaving 8 included reviews. Of the remaining 8 systematic reviews, only 1 was rated as high quality, [22] and the remaining were rated as acceptable. [13, 15, 23–27] One review updated evidence for piriformis syndrome, 1 evaluated a tool for central sensitization, 2 studies evaluated the diagnostic accuracy of orthopedic tests for SI joint pain, 2 addressed multiple conditions, and 2 assessed studies on lumbar radiculopathy and/or associated conditions. Supplemental Table 1 displays data abstracted from included studies. Key characteristics abstracted include study type, population size, age, symptom duration, diagnostic comparator, key findings, and key performance statistics.

Table 2

Table 2 [12, 30–55] displays the risk of bias assessment for individual studies. One study using Delphi methodology was unable to be assessed using the SIGN methodology checklist for diagnostic studies. [56]

 Diagnostic Categories

Nociceptive Pain. The International Association for the Study of Pain (IASP) defines nociceptive pain as “pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors.” [14] Nociceptive pain is caused by neural signaling in response to chemical (inflammatory), mechanical (tension or compression), and thermal stress. [57] In the low back, nociceptors are located within the major joints, ligaments, and myofascial tissues. [58, 59] Conditions consistent with nociceptive signaling (Fig 1) include the following:

(1) discogenic pain: pain from nociceptive signaling within the intervertebral disc [60];

(2) myofascial pain: pain from nociceptive signaling within muscle, tendon, and/or fascial tissues of the low back region;

(3) SI joint pain: pain from nociceptive signaling within and surrounding a SI joint [30]; and

(4) zygapophyseal (facet) joint pain: pain from nociceptive signaling within and surrounding a zygapophyseal (facet) joint. [60]

Discogenic Pain. This review identified 2 individual studies and 1 systematic review of diagnostic tests for discogenic pain. Tonosu et al reported that a score of 31 or higher on a 5–item differentially weighted questionnaire provided 1.0 sensitivity and 0.71 specificity for identifying discogenic pain using discography and response from decompression or fusion surgery to confirm a diagnosis. [54] Chan reported results of a Delphi process consensus study describing characteristics thought to represent pain from discal origin. [56] Petersen et al, in a systematic review, reported that evidence from several studies is sufficient to conclude that the centralization phenomenon is useful for identifying likely discogenic pain. Sensitivity in included studies ranged from 0.40 to 0.64, with specificity ranging from 0.70 to 0.95 with 2 studies reporting moderate to high positive likelihood ratios (6.9 and 9.4). [15]

Myofascial Pain. No individual studies assessing common myofascial pain diagnoses, such as muscle strain, were identified in this review. Petersen et al, in a systematic review, recommended that clinicians adopt diagnostic criteria consistent with the IASP definition of myofascial pain syndrome (palpable taut muscle region, hypersensitivity within taut muscle region with or without referred pain, and elicited pain reproduces familiar pain). [15] SI Joint Pain. Three systematic reviews and 5 separate articles assessed tests or studies designed to identify SI joint pain. [15, 22, 25, 37, 39, 44, 52, 55] Szadek et al reported that evidence does not support the use of individual pain provocation tests to identify probable SI joint pain. [25] Three systematic reviews separately concluded that available evidence supports a composite of 3 or more positive provocation tests (distraction, compression, thigh thrust, Gaenslen ’s left or right, and either sacral thrust or Patrick’s test) to suggest SI joint pain. [15, 22, 25]

Zygapophyseal (Facet) Joint Pain. Five studies and 1 systematic review assessed findings for facet joint pain. [15, 39, 40, 44, 46, 55] Diez-Ulloa et al, using anesthetic joint injection as the diagnostic comparison, reported that the positive and negative predictive value of the lordosis maneuver was 90% and 61%, respectively. [40] The lordosis maneuver begins in the prone position. The head and chest are actively raised, ending with weight-bearing on elbows and forearms without raising the pelvis. Mainka et al compared provocation maneuvers and imaging findings between symptomatic and asymptomatic age-matched controls with and without lumbar spine tenderness attributed to facet joint pain. [46] The authors concluded that pain provocation testing lacks specificity to be useful in accurately predicting facet joint pain. Petersen et al reported on 10 studies assessing diagnostic methods for identifying facet joint pain. No diagnostic decision rule was recommended. 15

Neuropathic Pain. The IASP defines neuropathic pain as “pain caused by a lesion or disease of the somatosensory nervous system.” [14] Neuropathic pain may occur separate from, or in conjunction with, nociceptive pain, potentially complicating the diagnostic process and demanding methods to differentiate one from the other.

Neuropathic pain associated with low back pain (Fig 1).

Neurogenic claudication: pain from intermittent compression and/or ischemia of a single or multiple nerve roots within an intervertebral foramen or the central spinal canal [61, 62]

Peripheral neuropathic pain: pain from inflammation, compression, or entrapment of peripheral nerves in the lumbar region [14, 63]

Radicular pain: pain from ectopic activation of nociceptors in a spinal nerve or its roots or from other mechanisms (eg, inflammation, tensile strain) [60]

Radiculopathy: objective sensory and/or motor function loss caused by conduction block in axons of a spinal nerve or its roots60

Sensitization: Increased responsiveness of nociceptive neurons to their normal input, and/or recruitment of a response to normally subthreshold inputs, [60] or a process of amplified peripheral and/or central nervous system pain signaling processes (central sensitization or peripheral sensitization). [14, 63, 64] Peripheral sensitization refers to reduced activation threshold among nociceptors in the periphery whereas central sensitization refers to similar changes among spinal cord and cerebral cortex neurons that process nociceptive signals. Central sensitization also involves additional neuroplastic/neuroadaptive processes. [63]

Ten studies assessed in-office methods for identifying or differentiating neuropathic from nociceptive pain. [31–35, 41, 42, 47, 51, 53] Available instruments include the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), S-LANSS (self-report version of LANSS), painDETECT questionnaire, McGill Pain Questionnaire, Standardized Evaluation of Pain tool, Douleur Neuropathique 4, ID Pain questionnaire, and Patient-Reported Outcome Measurement Information System Neuropathic Pain Quality Scale.

Neurogenic Claudication. One systematic review and 1 clinical study focused on neurogenic claudication were included. [49] Petersen et al offered a weak recommendation for using 3 or more of 5 possible findings to provide evidence for neurogenic claudication with a sensitivity of 0.29 and specificity of 0.88 (LRþ 2.5, LR– 0.80).

The 5 possible findings are

(1) age more than 48 years,

(2) bilateral symptoms,

(3) leg pain worse than low back pain,

(4) pain with walking/standing, and

(5) sitting relieves.

Nadeau et al assessed symptom characteristics for vascular and neurogenic claudication in a study using imaging, ankle brachial index measurements, and expert clinicians to confirm diagnoses and exclude individuals with both conditions. [49] Specific symptom constellations exhibited evidence for neurogenic claudication. Sensitivity and specificity for the presence of 2 symptoms (triggered with standing and relieved when sitting) were 0.80 and 0.87, respectively. Sensitivity and specificity for 3 symptoms (triggered with standing, relieved when sitting, located above knees) was 0.67 and 0.91, respectively. The addition of a positive shopping cart sign carried a sensitivity of 0.57 and specificity of 0.96. Positive likelihood ratios were 6.10, 7.70, and 13.00 for each successive combination (2, 3, and 4 symptoms).

Piriformis and Thoracolumbar Syndromes. One systematic review reported features from case studies to describe the frequency with which specific symptoms were reported by patients suspected to have piriformis syndrome. [23] The most frequently reported symptoms were radiating ipsilateral leg pain, greater sciatic notch tenderness, buttock pain, positive straight leg raise test (SLR), and pain while sitting. No data on the diagnostic accuracy of specific symptoms were identified. No articles reported on diagnosis for thoracolumbar syndrome, a condition of cluneal nerve entrapment causing low back and/or lower extremity pain. [65]

Radicular Pain. No studies in this review reported diagnostic methods for distinguishing between radicular pain and radiculopathy.

Radiculopathy. Three systematic reviews and 7 clinical studies evaluated methods for diagnosing lumbar radiculopathy. [12, 13, 15, 26, 33, 43, 45, 48, 50] Scaia et al synthesized evidence from 7 studies, reporting that the SLR demonstrated a wide range of sensitivity from 0.19 to 0.97 and specificity from 0.10 to 0.89, limiting diagnostic utility. [13] Tawa synthesized evidence from 12 studies reporting poor sensitivity of 0.13 to 0.61 for motor tests and sensitivity ranges of 0.14 to 0.67 and specificity of 0.60 to 0.93 for deep tendon reflexes. [26] Savage et al and Inal et al similarly reported poor relationships among symptom characteristics, exam findings, and nerve root conduction loss confirmed with electrodiagnostic testing. [43, 50] Petersen et al, in a review of 20 studies, reported sensitivity (0.28–0.50) and specificity (0.83–0.94) for a cluster of 3 or more of 4 findings in the presence of a positive SLR:

(1) pain in a dermatomal distribution,

(2) corresponding sensory deficit,

(3) diminished reflex, and

(4) motor weakness. [15]

Sensitization. Two included studies assessed central sensitization. [27, 38] No studies assessed peripheral sensitization. Scerbo et al, in a systematic review of studies using the Central Sensitization Inventory (CSI), reported high-quality evidence supporting psychometric properties and face validity, suggesting the instrument is useful in measuring central sensitization severity. [27] However, the authors note that the central sensitization was designed as a tool to measure the severity rather than diagnose central sensitization. Nijs et al, in a guideline for classifying neuropathic, nociceptive, and central sensitization pain, recommend practitioners use IASP criteria:

(1) low back pain experience disproportionate to the nature and extent of injury/pathology,

(2) neuroanatomically illogical pain pattern, and

(3) hypersensitivity of senses unrelated to the musculoskeletal system. [59]

We have provided an instructional video that provides an overview of this information (see video file online).

DISCUSSION

This systematic review summarizes and assesses studies reporting the diagnostic utility of clinical questionnaires, in-office tests, and patient or symptom characteristics to inform working diagnoses for common causes of LBP.

 Discogenic Pain

Provocation discography is the diagnostic reference standard test used to confirm discogenic pain. [66] Discography as a routine diagnostic procedure is not recommended owing to high cost; lack of standardized procedures; and risks such as subarachnoid puncture, discitis, allergic reaction, and chemical meningitis. [66] Similar to prior reviews, we conclude that current evidence supports the centralization phenomenon as an office-based test suggesting the presence of discogenic pain.

 Myofascial Pain

Table 3

The term myofascial pain is described as pain arising from hyperirritable foci within a muscle or related fascia or as a syndrome of muscle, sensory, motor, and autonomic symptoms associated with myofascial trigger points. [67, 68] Both descriptions refer to myofascial pain syndrome. However, the words myofascial pain simply imply pain arising from myofascial tissues. We recommend myofascial pain be defined as nociceptive signaling from within muscle or fascial tissues that may or may not include referred pain or the presence of trigger points (Table 3). [14, 15, 22, 31, 32, 35, 36, 41, 47, 51, 57, 60, 69, 70] This broader definition may reduce confusion caused by current descriptions, which instead of defining myofascial pain define myofascial pain syndrome. Diagnostic criteria consistent with this definition and with those recommended by Petersen et al include tenderness within a muscle with or without referred pain and reproduction of familiar pain with palpation or use. [15] The presence of hypersensitive areas (trigger points) is a criterion for myofascial pain syndrome, and thus not recommended as necessary for identifying the more general category of myofascial pain, which could include conditions such as muscle strain.

 SI Joint Pain

Despite the existence of numerous provocation tests designed to identify SI joint pain, current scientific evidence does not support the diagnostic utility of individual tests. Sacroiliac joint anesthetic injections (blocks) with a placebo or controlled comparative anesthetic are the current diagnostic standard. [22, 71] Sacroiliac joint blocks are not recommended for routine use owing to high cost, invasiveness, and associated risks. The prevalence of SI joint pain in persons with LBP ranges from 10% to 33%. [72] Intra-articular injection can only assess extra-articular pain when injectate leaks from the joint cavity, leaving potential extra-articular pain sources largely unstudied. Nevertheless, a composite of 3 or more maneuvers, which reproduce familiar pain, has diagnostic value. [15, 22, 25]

 Zygapophyseal (Facet) Joint Pain

The prevalence of facet joint pain ranges from 16% to 41% of persons with low back pain reported in studies using controlled anesthetic injection as the diagnostic standard. [73] A study by Laslett et al reported 3 or more of 5 possible findings (age over 50 years, onset paraspinal, pain relieved with walking, pain relieved with sitting, positive extension- rotation test) demonstrated a sensitivity of 0.85, a specificity of 0.91, a positive likelihood ratio of 9.7, and a 0.17 negative likelihood ratio. [69] Laslett et al conducted their study within a secondary/tertiary care setting and findings are yet to be reproduced. Thus, the evidence base for these criteria is currently weak, suggesting reported sensitivity, specificity, and likelihood ratios may be inflated. We recommend clinicians consider using criteria reported by Laslett et al, while recognizing the limitations of evidence obtained from a single study conducted in a specific setting. Adopting these diagnostic criteria has the advantage of identifying and describing patients with similar characteristics, which may have clinical utility.

 Nociceptive vs Neuropathic Pain

Distinguishing between nociceptive and neuropathic pain is important for informing clinical management strategies as evidenced by the numerous instruments designed to facilitate this distinction [31, 32, 34, 35, 36, 41, 42, 47, 51] and clinical guidelines recommending neuropathic pain identification. [59, 74–76] Research in this area has resulted in several office-based questionnaires, which exhibit acceptable psychometric properties, reliability, and face validity. [77, 78] Such instruments are derived from studies with a generally high risk of bias owing to the absence of reference standard diagnostic tests. Some instruments may not be effective as a screening tool in some subpopulations. For example, the painDETECT is not considered an effective screening tool for persons with chronic pain. [52] However, when used appropriately, these instruments can be useful. When neuropathic pain is potentially identified, further confirmation through neurologic exam, imaging, electrophysiology, or quantitative sensory testing may be required. [70, 74]

 Neurogenic Claudication

Neurogenic claudication occurs when spinal stenosis is severe enough to cause symptoms from intermittent neural compression or ischemia, most commonly from degenerative changes within the spine. [79, 80] We recommend diagnostic criteria reported by Nadeau et al. Constellations of 2, 3, or 4 symptoms (triggered with standing, relieved by sitting, symptoms above the knees, and positive shopping cart sign) exhibit progressively stronger evidence for the presence of neurogenic claudication with positive likelihood ratios of 6.10, 7.70, and 13.0, respectively. [49] The presence of symptoms occurring primarily above the knees is more consistent with neurogenic claudication, whereas symptoms primarily below the knees, when combined with relief upon standing, more likely identify vascular claudication. [49] Alternatively, 3 or more of 5 criteria also show diagnostic utility, though exhibiting lower sensitivity and specificity:

(1) age more than 48 years,

(2) bilateral symptoms,

(3) leg pain worse than low back pain,

(4) pain with walking/standing, and

(5) sitting relieves pain. [15]

 Piriformis and Thoracolumbar Syndromes

Piriformis and thoracolumbar syndromes are subtypes of peripheral neuropathic pain. Piriformis syndrome is caused by compression, entrapment, or inflammation of the sciatic nerve, from direct piriformis muscular impingement or other mechanisms. [81]

Current diagnostic criteria are available only through a systematic review of clinical features reported in the scientific literature:

(1) ipsilateral leg radiation,

(2) greater sciatic notch tenderness,

(3) buttock pain,

(4) positive SLR, and

(5) pain with sitting. [23]

No included articles reported on studies assessing diagnostic criteria for thoracolumbar syndrome originally described by Maigne:

(1) pain in nerve distribution (iliac crest, groin, or greater trochanter),

(2) trigger point over iliac crest approximately 7 cm from midline,

(3) sensitivity to iliac crest skin rolling, and

(4) tenderness of 1 or more thoracolumbar spinous processes or facet joints. [65, 82, 83]

 Radicular Pain and Radiculopathy

Table 4

Several studies focused on identifying radiculopathy or sciatica, reporting wide variations in sensitivity and specificity of tests such as the SLR. [13, 15, 26] The absence of convincing evidence for diagnostic accuracy is due to several methodological limitations shared by many included studies, most notably by using different methods to conduct or interpret tests, by considering radicular pain and radiculopathy as a singular condition, and by presuming imaging is an adequate reference standard for radiculopathy. [12, 13, 26, 33, 43, 50, 45, 48, 84] Imaging cannot confirm whether nerve root compression is of sufficient intensity to cause reduced neural signaling, which is the necessary element for radiculopathy. Therefore, participants in studies using imaging confirmation of nerve root compression probably comprise those with radicular pain and those with radiculopathy. In the absence of conclusive diagnostic studies, we recommend practitioners use IASP criteria for discriminating between radiculopathy or radicular pain (Table 4). [14, 23, 49, 59, 60, 65, 82]

 Sensitization

Research in this area is generally limited by the absence of an objective standard diagnostic test resulting in questionnaire instruments that assess neuropathic or nociceptive pain based on expert consensus criteria or codified into clinical guidelines. [58] We recommend practitioners adopt the IASP criteria as recommended in a recent clinical guideline (Table 4). [59]

 Quality

Most individual studies included in this review contained a high risk of bias in the reference standard domain. This finding is expected because most conditions causing LBP lack high-quality reference standard tests that can definitively confirm or rule out their presence. Patient selection bias was another common domain designated with a high risk for bias among individual included studies. Both factors have the potential to bias results toward overestimation of diagnostic test accuracy (Table 2).

 Terminology Recommendations

Studies included in this review refer to pain of radicular origin using disparate and nondescript terms. For example, Ohnmeiss et al reported examining the relationship between pain drawings and discogenic pain. [12] However, radicular pain, rather than discogenic pain (pain from nociceptive signaling within the intervertebral disc), was studied. Scaia et al, in a systematic review of studies evaluating diagnostic methods for sciatica and disc herniation, concluded that poor test utility may result from studying separate conditions that sometimes share similar characteristics, confounding diagnostic accuracy results. [13]

Radicular pain occurs with ectopic neural transmission generated from inflammation or other insult, such as mechanical stress. In contrast, the hallmark of radiculopathy is nerve conduction loss. [60] However, no study included in this review distinguished these 2 conditions. Such study designs are likely to report poor diagnostic utility of studied criteria as observed in this review. Similarly, neurogenic claudication was commonly referred to as lumbar stenosis. [15] Though some included reviews reported evaluating diagnostic criteria for myofascial pain, myofascial pain syndrome was the condition of focus. [15]

To avoid the unnecessary complexity and confusion created by multiple overlapping and nonspecific terms, adoption of IASP applicable terminology across professions and within scientific publications is strongly recommended. [14, 60] Standardized terminology adoption fosters clear communication between and among health professionals, researchers, and patients, and uses evidence-based terminology that directly relates to underlying physiology. Diagnoses with IASP-established definitions included in this review include radiculopathy, radicular pain, sensitization, peripheral neuropathic pain, discogenic pain, SI joint pain, and facet joint pain (Tables 3 and 4). Piriformis syndrome, thoracolumbar syndrome, neurogenic claudication, and myofascial pain are not specifically defined by the IASP. Consistent with IASP terminology, piriformis and thoracolumbar syndrome represent peripheral neuropathic pain subtypes as defined by the IASP. Likewise, myofascial pain describes nociceptive firing from within myofascial tissues, among which subtypes, such as myofascial pain syndromes and muscle strain, exist (Table 3). Neurogenic claudication has been described as a clinical syndrome resulting from neurologic compression or ischemia caused by spinal stenosis. [61, 62, 85, 86] However, because persons with spinal stenosis may not experience neurogenic claudication symptoms, using the term spinal stenosis to describe neurogenic claudication is inaccurate and potentially labels patients with benign conditions, contributing to unnecessary morbidity.

Limitations

All systematic reviews are limited by search strategy, which may not be comprehensive. In this review, multiple searches using a variety of terms for included diagnoses were used. Including other systematic reviews with alternate search strategies was also designed to mitigate this limitation. We used standardized instruments to conduct article quality assessment. Although quality assessment was performed by experienced researchers, judgment and interpretation are necessary and there exists no established value separating high-, moderate, and low-quality studies. Many included studies enrolled participants in secondary or tertiary care settings, limiting generalizability to primary spine care settings. The absence of objective reference standard tests limits scientific evaluation for several conditions studied in this review. In such instances, expert recommendations describing diagnostic criteria represent the best available evidence. Such diagnostic criteria are supported by current scientific understanding of physiology, although they lack stronger validation. As evidence evolves, additional literature review will be needed to summarize and update information on this topic. Finally, study heterogeneity prevented data pooling.

CONCLUSION

This review describes evidence-based diagnostic criteria for common conditions contributing to neuromusculoskeletal low back pain. Understanding the accuracy of tests and the evidence basis from which diagnostic criteria are derived can inform management decisions and the amount of confidence placed in a working diagnosis. Adopting IASP-applicable terminology is recommended to improve communication among health professionals, patients, and researchers, and to improve the quality of diagnosis-related research.

Practical Applications

This systematic review summarizes and describes the type of scientific evidence supporting diagnostic criteria for common causes of LBP.

The review also highlights and describes problems with current disparate terminology use and how this practice is hindering research efforts and causing confusion for clinicians and researchers.

Formal recommendations for standardizing terminology are included.

ACKNOWLEDGMENTS

The authors thank Anna Schmidt, MM, DC, for reviewing manuscript drafts, providing critical feedback, and performing other activities relevant to this project.

FUNDING SOURCES AND CONFLICTS OF INTEREST

Drs Vining, Shannon, Minkalis, and Twist report grant support from the National Institutes of Health/National Center for Complementary & Integrative Health 5UG3AT009761-02. Dr Shannon reports support from the NCMIC Foundation. No funding agency was involved in data collection, data analysis, data interpretation, or manuscript writing. No other conflicts of interest were reported for this study.

CONTRIBUTORSHIP INFORMATION

Concept development (provided idea for the research): R.V.

Design (planned the methods to generate the results): R.V., A.M., Z.S., E.T.

Supervision (provided oversight, responsible for organization and implementation, writing of the manuscript): R.V.

Data collection/processing (responsible for experiments, patient management, organization, or reporting data): Z.S., E.T., A.M., R.V.

Analysis/interpretation (responsible for statistical analysis, evaluation, and presentation of the results): R.V., Z.S., A.M., E.T.

Literature search (performed the literature search): A.M. Writing (responsible for writing a substantive part of the manuscript): R.V., A.M., E.T.

Critical review (revised manuscript for intellectual content, this does not relate to spelling and grammar checking): R.V., A.M., Z.S., E.T.

References:

Shmagel A, Foley R, Ibrahim H.

Epidemiology of Chronic Low Back Pain in US Adults: Data From

the 2009-2010 National Health and Nutrition Examination Survey

Arthritis Care Res (Hoboken) 2016 (Nov); 68 (11): 1688–1694

Deyo RA, Dworkin SF, Amtmann D, et al.

Report of the National Institutes of Health task force on research standards for chronic low back pain.

J Manipulative Physiol Ther. 2014; 37(7):449-467.

Simmonds N, Miller P, Gemmell H.

A theoretical framework for the role of fascia in manual therapy.

J Bodyw Mov Ther. 2012;16(1):83-93.

Stynes S, Konstantinou K, Dunn KM.

Classification of patients with low back-related leg pain: a systematic review.

BMC Musculoskelet Disord. 2016;17:226.

Brennan GP, Fritz JM, Hunter SJ, Thackeray A, Delitto A, Erhard RE.

Identifying subgroups of patients with acute/subacute “nonspecific” low back pain:

results of a randomized clinical trial.

Spine (Phila Pa 1976). 2006;31(6):623-631.

Fritz JM, Lindsay W, Matheson JW, et al.

Is there a subgroup of patients with low back pain likely to benefit from mechanical traction?

Results of a randomized clinical trial and subgrouping analysis.

Spine (Phila Pa 1976). 2007; 32(26):E793-E800.

Negrini S, Zaina F.

The chimera of low back pain etiology: a clinical rehabilitation perspective.

Am J Phys Med Rehabil. 2013;92(1):93-97.

Adler RH.

Engel’s biopsychosocial model is still relevant today.

J Psychosom Res. 2009;67(6):607-611.

R.A. Deyo, S.F. Dworkin, D. Amtmann, G. Andersson, et al.,

Report of the NIH Task Force on Research Standards for Chronic Low Back Pain

Journal of Pain 2014 (Jun); 15 (6): 569–585

Maher C, Underwood M, Buchbinder R.

Non-specific low back pain.

Lancet. 2017;389(10070):736-747.

Waddell G.

Subgroups within “nonspecific” low back pain.

J Rheumatol. 2005;32(3):395-396.

Ohnmeiss DD, Vanharanta H, Ekholm J.

Relationship of pain drawings to invasive tests assessing intervertebral disc pathology.

Eur Spine J. 1999;8(2):126-131.

Scaia V, Baxter D, Cook C.

The pain provocation-based straight leg raise test for diagnosis of lumbar disc herniation,

lumbar radiculopathy, and/or sciatica: a systematic review of clinical utility.

J Back Musculoskelet Rehabil. 2012;25(4): 215-223.

International Association for the Study of Pain.

IASP terminology. Available at:

https://s3.amazonaws.com/rdcms-iasp/files/production/public/Content/ContentFolders/Publications2/

ClassificationofChronicPain/Part\_II-G.pdf

Accessed November 5, 2018.

Petersen T, Laslett M, Juhl C.

Clinical Classification in Low Back Pain: Best-evidence Diagnostic Rules Based on Systematic Reviews

BMC Musculoskelet Disord. 2017 (May 12); 18 (1): 188

Kalichman L, Cole R, Kim DH, et al.

Spinal stenosis prevalence and association with symptoms: the Framingham Study.

Spine J. 2009;9(7):545-550.

Vining R, Potocki E, Seidman M, Morgenthal AP.

An Evidence-based Diagnostic Classification System For Low Back Pain

J Canadian Chiropractic Assoc 2013 (Sep); 57 (3): 189–204

Vining RD, Minkalis AL, Shannon ZK, Twist EJ.

Development of an Evidence-Based Practical Diagnostic Checklist

and Corresponding Clinical Exam for Low Back Pain

J Manipulative Physiol Ther. 2019 (Nov); 42 (9): 665–676

Vining RD, Shannon ZK, Salsbury SA, Corber L, Minkalis AL, Goertz CM.

Development of a Clinical Decision Aid for Chiropractic Management

of Common Conditions Causing Low Back Pain in Veterans:

Results of a Consensus Process

J Manipulative Physiol Ther. 2019 (Nov); 42 (9): 677–693

Moher D, Liberati A, Tetzlaff J, Altman DG.

Preferred Reporting Items for Systematic Reviews

and Meta-Analyses: The PRISMA Statement

PLoS Medicine 2009 (Jul 21); 6 (7): e1000100

Furlan AD, Malmivaara A, Chou R, et al.

2015 updated method guideline for systematic reviews in the Cochrane Back and Neck Group.

Spine (Phila Pa 1976). 2015;40(21):1660-1673.

Simopoulos T, Manchikanti L, Singh V, et al.

A systematic evaluation of prevalence and diagnostic accuracy of sacroiliac joint interventions.

Pain Physician. 2012;15(3):E305-E344.

HopayianK, Danielyan A.

Four symptoms define the piriformis syndrome: an updated systematic review of its clinical features.

Eur J Orthop Surg Traumatol. 2018;28(2):155-164.

Simpson R, Gemmell H.

Accuracy of spinal orthopaedic tests: a systematic review.

Chiropr Osteopat. 2006;14:26.

Szadek KM, van der Wurff P, van Tulder MW, Zuurmond WW, Perez RS.

Diagnostic validity of criteria for sacroiliac joint pain: a systematic review.

J Pain. 2009; 10(4):354-368.

Tawa N, Rhoda A, Diener I.

Accuracy of clinical neurological examination in diagnosing lumbo-sacral radiculopathy:

a systematic literature review.

BMC Musculoskelet Disord. 2017;18(1):1-11.

Scerbo T, Colasurdo J, Dunn S, Unger J, Nijs J, Cook C.

Measurement properties of the central sensitization inventory: a systematic review.

Pain Pract. 2018;18(4):544-554.

Vroomen PCAJ, de Krom MC, Knottnerus JA.

Diagnostic value of history and physical examination in patients suspected of sciatica due to

disc herniation: a systematic review.

J Neurol. 1999;246(10):899-906.

van den Hoogen HM, Koes BW, van Eijk JT, Bouter LM.

On the accuracy of history, physical examination, and erythrocyte sedimentation rate in diagnosing

low back pain in general practice. A criteria-based review of the literature.

Spine. 1995;20(3):318-327.

Adelmanesh F, Jalali A, Shirvani A, et al.

The diagnostic accuracy of gluteal trigger points to differentiate radicular from nonradicular low back pain.

Clin J Pain. 2016;32(8): 666-672.

Askew RL, Cook KF, Keefe FJ, et al.

A PROMIS measure of neuropathic pain quality.

Value Health. 2016;19(5):623-630.

Attal N, Perrot S, Fermanian J, Bouhassira D.

The neuropathic components of chronic low back pain: a prospective multicenter study

using the DN4 questionnaire.

J Pain. 2011; 12(10):1080-1087.

Beattie PF, Meyers SP, Stratford P, Millard RW, Hollenberg GM.

Associations between patient report of symptoms and anatomic impairment visible on

lumbar magnetic resonance imaging.

Spine (Phila Pa 1976). 2000; 25(7):819-828.

Bennett M.

The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs.

Pain. 2001;92(1-2):147-157.

Bennett MI, Smith BH, Torrance N, Lee AJ.

Can pain can be more or less neuropathic? Comparison of symptom assessment tools with ratings

of certainty by clinicians.

Pain. 2006; 122(3):289-294.

Bouhassira D, Attal N, Alchaar H, et al.

Comparison of pain syndromes associated with nervous or somatic lesions and development of a new

neuropathic pain diagnostic questionnaire (DN4).

Pain. 2005;114(1-2):29-36.

Cibulka MT, Koldehoff R.

Clinical usefulness of a cluster of sacroiliac joint tests in patients with and without low back pain.

J Orthop Sports Phys Ther. 1999;29(2):83-92.

Defrin R, Devor M, Brill S.

Tactile allodynia in patients with lumbar radicular pain (sciatica).

Pain. 2014;155(12):2551-2559.

Depalma MJ, Ketchum JM, Trussell BS, Saullo TR, Slipman CW.

Does the location of low back pain predict its source?

PM R. 2011;3(1):33-39.

Díez-Ulloa M, Almira Suarez E, Otero Fernandez M, Leborans Eiras S.

Lordosis manoeuvre in the diagnosis of lumbar facet syndrome.

Rev Esp Cir Ortop Traumatol. 2016;60(4):221-226.

Dworkin RH, Turk DC, Trudeau JJ, et al.

Validation of the short-form McGill pain questionnaire-2 (SF-MPQ-2) in acute low back pain.

J Pain. 2015;16(4):357-366.

Freynhagen R, Baron R, Gockel U, T€olle TR.

Pain DETECT: a new screening questionnaire to identify neuropathic components in patients with back pain.

Curr Med Res Opin. 2006;22(10):1911-1920.

Inal EE, Eser F, Aktekin LA, Eoksuz E, Bodur H.

Comparison of clinical and electrophysiological findings in patients with suspected radiculopathies.

J Back Musculoskelet Rehabil. 2013;26(2):169-173.

Jung J-H, Kim H-I, Shin D-A, et al.

Usefulness of pain distribution pattern assessment in decision-making for the patients with lumbar

zygapophyseal and sacroiliac joint arthropathy.

J Korean Med Sci. 2007;22(6):1048-1054.

Konstantinou K, Lewis M, Dunn KM.

Agreement of selfreported items and clinically assessed nerve root involvement (or sciatica)

in a primary care setting.

Eur Spine J. 2012; 21(11):2306-2315.

Mainka T, Lemburg SP, Heyer CM, Altenscheidt J, Nicolas V, Maier C.

Association between clinical signs assessed by manual segmental examination and findings of the lumbar facet

joints on magnetic resonance scans in subjects with and without current low back pain:

a prospective, single-blind study.

Pain. 2013;154(9):1886-1895.

Mayoral V, Perez-Hernandez C, Muro I, Leal A, Villoria J, Esquivias A.

Diagnostic accuracy of an identification tool for localized neuropathic pain based on the IASP criteria.

Curr Med Res Opin. 2018;34(8):1465-1473.

Murphy DR, Hurwitz EL, Gerrard JK et al.

Pain Patterns and Descriptions in Patients with Radicular Pain:

Does the Pain Necessarily Follow a Specific Dermatome?

Chiropractic & Osteopathy 2009 (Sep 21); 17 (1): 9

Nadeau M, Rosas-Arellano MP, Gurr KR, et al.

The reliability of differentiating neurogenic claudication from vascular claudication based on

symptomatic presentation.

Can J Surg. 2013;56(6):372-377.

Savage NJ, Fritz JM, Thackeray A.

The relationship between history and physical examination findings and the outcome of electrodiagnostic

testing in patients with sciatica referred to physical therapy.

J Orthop Sports Phys Ther. 2014;44(7):508- 517.

Scholz J, Mannion RJ, Hord DE, et al.

A novel tool for the assessment of pain: validation in low back pain.

PLoS Med. 2009;6(4), e1000047.

Shimpi A, Hatekar R, Shyam A, Sancheti P.

Reliability and validity of a new clinical test for assessment of the sacroiliac joint dysfunction.

Hong Kong Physiother J. 2018;38(1): 13-22.

Timmerman H, Wolff AP, Bronkhorst EM, et al.

Avoiding Catch-22: validating the PainDETECT in a in a population of patients with chronic pain.

BMC Neurol. 2018;18(1):91.

Tonosu J, Inanami H, Oka H, et al.

Diagnosing discogenic low back pain associated with degenerative disc disease using a medical interview.

PLoS One. 2016;11(11):1-9.

Young S, Aprill C.

Characteristics of a mechanical assessment for chronic lumbar facet joint pain.

J Man Manip Ther. 2000; 8(2):78-84.

Chan AYP, Ford JJ, McMeeken JM, Wilde VE.

Preliminary evidence for the features of non-reducible discogenic low back pain: survey of an

international physiotherapy expert panel with the Delphi technique.

Physiotherapy. 2013;99(3): 212-220.

Smart KM, Blake C, Staines A, Thacker M, Doody C.

Mechanisms-based classifications of musculoskeletal pain: part 3 of 3:

symptoms and signs of nociceptive pain in patients with low back (±leg) pain.

Man Ther. 2012;17(4): 352-357.

Youssef P, Loukas M, Chapman JR, Oskouian RJ, Tubbs RS.

Comprehensive anatomical and immunohistochemical review of the innervation of the human spine and joints

with application to an improved understanding of back pain.

Childs Nerv Syst. 2016;32(2):243-251.

Nijs J., Apeldoorn A., Hallegraeff H., et al.

Low Back Pain: Guidelines for the Clinical Classification of

Predominant Neuropathic, Nociceptive, or

Central Sensitization Pain

Pain Physician. 2015 (May); 18 (3): E333–346

International Association for the Study of Pain.

Spinal pain, section 1: spinal and radicular pain syndromes. Available at:

https://s3.amazonaws.com/rdcms-iasp/files/production/public/Content/ContentFolders/

Publications2/ClassificationofChronicPain/PART\_I-C.pdf

Accessed November 5, 2018.

Maus TP.

Imaging of spinal stenosis: neurogenic intermittent claudication and cervical spondylotic myelopathy.

Radiol Clin North Am. 2012;50(4):651-679.

Katz JN, Harris MB.

Lumbar spinal stenosis.

N Engl J Med. 2008;358(8):818-825.

Costigan M, Scholz J, Woolf CJ.

Neuropathic pain: a maladaptive response of the nervous system to damage.

Annu Rev Neurosci. 2009;32:1-32.

Woolf CJ.

Central sensitization: implications for the diagnosis and treatment of pain.

Pain. 2011;152(3 suppl):S2-S15.

Maigne JY, Doursounian L.

Entrapment neuropathy of the medial superior cluneal nerve.

Spine (Phila Pa 1976). 1997; 22(10):1156-1159.

Manchikanti L, Benyamin RM, Singh V, et al.

An update of the systematic appraisal of the accuracy and utility of lumbar discography in chronic

low back pain.

Pain Physician. 2013; 16(2 suppl):SE55-SE95.

Bennett R.

Myofascial pain syndromes and their evaluation.

Best Pract Res Clin Rheumatol. 2007;21(3):427-445.

Stecco A, Gesi M, Stecco C, Stern R.

Fascial components of the myofascial pain syndrome.

Curr Pain Headache Rep. 2013;17(8):352.

Laslett M, McDonald B, Aprill CN, Tropp H, Oberg B.

Clinical predictors of screening lumbar zygapophyseal joint blocks: development of clinical prediction rules.

Spine J. 2006;6(4):370-379.

Bennett MI, Attal N, Backonja MM, et al.

Using screening tools to identify neuropathic pain.

Pain. 2007;127(3):199-203.

Rupert MP, Lee M, Manchikanti L, Datta S, Cohen SP.

Evaluation of sacroiliac joint interventions: a systematic appraisal of the literature.

Pain Physician. 2009; 12(2):399-418.

Kennedy DJ, Engel A, Kreiner DS, Nampiaparampil D, Duszynski B, MacVicar J.

Fluoroscopically guided diagnostic and therapeutic intra-articular sacroiliac joint injections:

a systematic review.

Pain Med. 2015;16(8):1500-1518.

Boswell MV, Manchikanti L, Kaye AD, et al.

A best-evidence systematic appraisal of the diagnostic accuracy and utility of facet (zygapophysial)

joint injections in chronic spinal pain.

Pain Physician. 2015;18(4):E497-E533.

Haanp€a€a M, Attal N, Backonja M, et al.

NeuPSIG guidelines on neuropathic pain assessment.

Pain. 2011; 152(1):14-27.

Qaseem A, Wilt TJ, McLean RM, Forciea MA;

Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain:

A Clinical Practice Guideline From the American College of Physicians

Annals of Internal Medicine 2017 (Apr 4); 166 (7): 514–530

The Diagnosis and Treatment of Low Back Pain Work Group.

VA/DoD Clinical Practice Guideline for Diagnosis and Treatment of Low Back Pain PDF

Washington, DC: The Office of Quality, Safety and Value, VA, &

Office of Evidence Based Practice, U.S. Army MedicalCommand, 2017, Version 2.0.

Jones 3rd RC, Backonja MM.

Review of neuropathic pain screening and assessment tools.

Curr Pain Headache Rep. 2013;17(9):363.

Walsh J, Rabey MI, Hall TM.

Agreement and correlation between the self-report Leeds assessment of neuropathic symptoms and signs

and Douleur Neuropathique 4 Questions neuropathic pain screening tools in subjectswith low back-related leg pain.

J Manipulative Physiol Ther. 2012;35(3):196-202.

Modic MT, Ross JS.

Lumbar degenerative disk disease.

Radiology. 2007;245(1):43-61.

Suri P, Rainville J, Kalichman L, Katz JN.

Does this older adult with lower extremity pain have the clinical syndrome of lumbar spinal stenosis?

JAMA. 2010;304(23):2628-2636.

Michel F, Decavel P, Toussirot E, et al.

The piriformis muscle syndrome: an exploration of anatomical context, pathophysiological hypotheses

and diagnostic criteria.

Ann Phys Rehabil Med. 2013;56(4):300-311.

Alptekin K, €Ornek NI, Aydõn T, et al.

Effectiveness of exercise and local steroid injections for the thoracolumbar junction syndrome

(the Maigne’s syndrome) treatment.

Open Orthop J. 2017;11(1):467-477.

DiMond ME.

Rehabilitative principles in the management of thoracolumbar syndrome: a case report.

J Chiropr Med. 2017; 16(4):331-339.

Rashbaum RF, Ohnmeiss DD, Lindley EM, Kitchel SH, Patel VV.

Sacroiliac joint pain and its treatment.

Clin Spine Surg. 2016;29(2):42-48.

Atlas SJ, Delitto A.

Spinal stenosis: surgical versus nonsurgical treatment.

Clin Orthop. 2006;443:198-207.

Porter R.

Spinal stenosis and neurogenic claudication.

Spine (Phila Pa 1976). 1996;21(17):2046-2052.