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REVIEW

Mapping guideline-informed care for chronic non-specific low back pain with the biopsychosocial approach: A rapid review

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Abstract

Background: Current evidence favors a multidisciplinary biopsychosocial approach to the management of chronic non-specific low back pain (CLBP). However, it is unclear whether such an approach is facilitated by current clinical guidelines. This rapid review set out to examine the extent to which clinical guideline recommendations for managing CLBP address domains of the biopsychosocial approach.

Methods: MEDLINE, EMBASE, CINAHL, and the gray literature were searched for any clinical guidelines targeting the management of CLBP, published within the last 6 years. Title/abstract and full-text screening were undertaken by two reviewers using the accelerated approach. Data extraction and critical appraisal were completed by two reviewers, independently. Extracted data were synthesized in narrative form.

Results: Fifteen guidelines met the review inclusion criteria. One-half of the guidelines were considered to be of medium quality. All guidelines provided management recommendations addressing the biological domain of the biopsychosocial approach; 13 (87%) guidelines reported recommendations addressing the psychological domain, and 8 (53%) guidelines presented recommendations addressing the social domain. Only 53% (8/15) of guidelines reported recommendations addressing all three domains of the biopsychosocial approach. Guideline recommendations both across and within the biopsychosocial domains were varied and inconsistent.

Conclusions: The CLBP clinical guidelines included in this review provided detailed guidance on the biological domain, yet limited attention and detail were afforded to the psychological and social domains. Several recommendations are presented on how to improve the quality of future CLBP guidelines, and to help foster the provision of a biopsychosocial approach to CLBP management.

KEYWORDS

biopsychosocial model, clinical guidelines, low back pain, multidisciplinary care, review

INTRODUCTION

Chronic non-specific low back pain (CLBP) is defined as persistent pain in the lower back for a period exceeding 3 months, for which there is no clear pathoanatomical cause.¹ The personal and societal impacts of CLBP are considerable, with CLBP affecting 38.9% of the global adult population²; higher lifetime prevalence rates have been reported in Australia (79.2%),³ and regional areas.⁴ The high prevalence and chronicity of CLBP place significant demand on healthcare systems, with CLBP being among the most frequently

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reported conditions presenting to primary care, globally.⁵

CLBP is also a leading cause of global disability,⁶ accounting for 60.1 million years lived with disability in 2015.⁷ Anxiety, depression, sleep disorders, limited physical activity, and reduced quality of life are significantly associated with CLBP also.^{8,9} These comorbidities, and their management, add to the complexity and burden of CLBP.

Myriad factors have been reported to contribute to the onset, severity, and persistence of CLBP. Most of these factors are modifiable, and include psychological stress and distress, depression, overweight/obesity, smoking, sleep disturbances, and biomechanical stress.^{1,10} Accordingly, a multidisciplinary biopsychosocial approach to CLBP management has been advocated in recent years. Findings from several systematic reviews have indicated that a multidisciplinary biopsychosocial approach is clinically effective and cost-effective (when compared with usual care or physical treatments) in improving pain, disability, and return to work in patients with CLBP.^{11,12} A multidisciplinary biopsychosocial approach also aligns with the healthcare needs of people seeking care for CLBP, including the need for improvement in biological (eg, pain, activity limitations), psychological (eg, mood, quality of life), and social (eg, work, social activities) outcomes.¹³

Clinical guidelines typically represent best-practice care, and are intended to facilitate clinical decisionmaking regarding CLBP management. However, it is unclear whether these guidelines foster the provision of a multidisciplinary biopsychosocial approach to CLBP care. Endorsing such an approach is not only integral to addressing unmet patient needs, but also improving patient outcomes. Poor access to best-practice multidisciplinary care for chronic pain has been shown to be associated with increased opioid use, greater healthcare costs, poorer health outcomes, and reduced patient satisfaction.¹⁴ Given the increasing focus on the multidisciplinary biopsychosocial approach for CLBP care, we set out to examine the extent to which clinical guideline recommendations for managing CLBP address domains of the biopsychosocial approach.

METHODS

Design

Rapid review.

Selection criteria

The search considered all clinical practice guidelines targeting the management of CLBP. We defined clinical guidelines as "statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options".¹⁵ Excluded were reviews of guidelines, and guidelines focusing only upon CLBP prevention, screening, diagnosis, classification, or a single treatment modality (eg, spinal manipulation only). Guidelines targeting a specific subpopulation of patients with CLBP, patients with acute or subacute LBP, were a synthesis or summary of guidelines, or were superseded by more recent guidelines released by the same organization were excluded also.

Search strategy

The following bibliographic databases were searched for relevant guidelines: MEDLINE, EMBASE, and CINAHL. The gray literature was also searched; specifically, the websites of relevant national health research authorities (ie, National Health & Medical Research Council. Australia: National Institute of Health. US: National Institute for Clinical Excellence, UK), national guideline repositories (ie, National Guideline Clearing House, US; Guideline International Network, Germany; National library of Guidelines, UK; Canadian Agency for Drugs and Technologies in Health, Canada) and national professional pain associations (ie, Australian Pain Society; American Pain Association; British Pain Society). The search was limited to guidelines published in the English language, and within the last 6 years (ie, from 2016 to December 2022), to ensure guidelines represented contemporary best practice care.

Search terms included:

- 1. algorithm OR clinical protocol OR guidelines OR practice guidelines
- 2. back pain OR back ache OR low* back pain OR low* back ache OR nonspecific back pain OR lumbago.
- 3. 1 AND 2

A Google scholar search was also conducted using "chronic non-specific back pain AND clinical practice guidelines" as search terms, with the number of results limited to the first 10 pages.

Screening

The search was conducted by TA. References were imported into EndNote X9 (Clarivate) for duplicate removal, with remaining references imported into Covidence (Veritas Health Innovation) for screening. Title and abstract screening were undertaken by TA. In accordance with the accelerated approach, 20% of screened results were cross-checked by ML. Any disagreements were resolved by discussion. The same process was followed for full-text screening.

Data extraction

Data were extracted from included studies by ML and TA, using a customized data extraction tool, with any disagreements resolved by discussion. The tool gathered the following information: author, year, country, endorsement agency (ie, national research authority, national association/society, professional association), management recommendations by biopsychosocial domain (ie, biological, psychological, social), coverage of biopsychosocial domains (ie, proportion of the three domains that were clearly presented within the guideline to any level of detail), and depth of content (ie, proportion of the four domains that contained high-level information [ie, provided a detailed discussion of the elements within the domain]) (Table 1).

Critical appraisal

The Appraisal of Guidelines for Research and Evaluation Global Rating Scale (AGREE GRS)¹⁶ was used to assess the quality of included guidelines. The AGREE GRS comprises seven items that assess process of development, presentation style, completeness of reporting, clinical validity, overall quality, recommending guideline, and utilizing guideline. All criteria were rated on a 7-point Likert scale, with the first five criteria using 1 = lowest quality and 7 = highest quality as anchors, and the latter two criteria using 1 = strongly disagree and 7 = strongly agree as anchors. Critical appraisal was undertaken by ML and TA, with any disagreements resolved by discussion.

Statistical analysis

Extracted data were synthesized in narrative form due to the descriptive nature of the review outcomes.

RESULTS

Search results

The search identified 2310 records (Figure 1). Following the removal of duplicates (n = 144), and the exclusion of ineligible records at the title and abstract screening stage

(n = 2144), 22 records were retrieved for full-text screening. Seven records were not eligible for inclusion as they were beyond the scope of the review (n = 5) or were not accessible (n = 2). A total of 15 guidelines met the inclusion criteria for this review.

Characteristics of included guidelines

All guidelines were published within the past 6 years, with 60% (9/15) published between 2016 and 2019 (Table 2). The majority of included guidelines were developed by North American (n = 7) and UK/European (n = 4) collaborations, followed by Korean (n = 1), Japanese (n = 1), and Russian (n = 1) collaborations; one guideline was developed by a global initiative. The guidelines were mostly endorsed by health societies and institutes (n = 5), health authorities (n = 4), and cross-institutional collaborations (ie, combination of universities, authorities, and institutes/societies) (n = 5), with one guideline endorsed by a university (n = 1).

All 15 guidelines provided management recommendations addressing the biological domain of the biopsychosocial approach; 13 (87%) of the guidelines reported recommendations addressing the psychological domain, and 8 (53%) of the guidelines presented recommendations addressing the social domain (Table 2). Only 53% (8/15) of included guidelines reported recommendations addressing all three domains of the biopsychosocial approach.¹⁷⁻²⁴

Quality of included guidelines

The included guidelines were assessed for quality against the seven AGREE GRS criteria (Table 3). In relation to the "process of development," most (n = 9, 60%) guidelines were considered to be medium quality (scoring between 3 and 5 on a 7-point scale),^{17,19,24–30} with four (27%) guidelines rated as high quality (scoring 6 or 7)^{18,20,21,23} and two rated as low quality (scoring 1 or 2).^{22,31} For "presentation style," four guidelines were considered to be high quality,^{17,20,23,25} three considered to be low quality,^{22,26,31} and the remaining eight rated as medium qual ity.^{18,19,21,24,27–30}

In terms of "completeness of reporting," eight guidelines were rated as medium quality,^{18,19,21,24,26,28–30} four

TABLE 1 Elements of each domain of the biopsychosocial approach that impact the management of CLBP.^{49,50}

Domain	Elements
Biological	Age; biomechanics; comorbidity; gender; genetics; metabolic factors; neurochemistry; pathophysiology; physical disability; severity of disease
Psychological	Addictions; attitudes/beliefs; cognitive factors; developmental issues; expectations; literacy/health literacy; mental illness; past experiences; personality; preferences; psychological stress; readiness to change; self-efficacy; self-esteem
Social	Economic factors; employment/occupation; environment/geography; ethnicity/culture/race; family/social support and relationships; health provider/system factors; housing; language proficiency

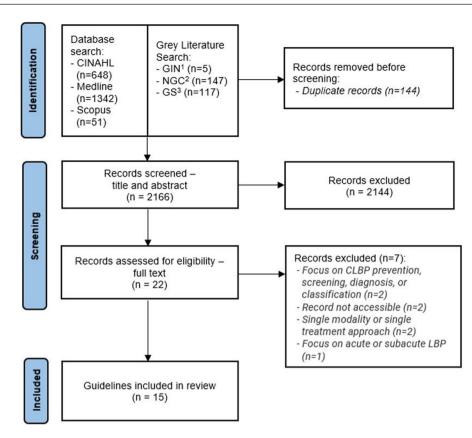


FIGURE 1 Review flow chart. CLBP, chronic non-specific low back pain. ¹Guideline International Network. ²National Guideline Clearinghouse. ³Google Scholar.

as high quality,^{17,20,23,25} and three as low quality.^{22,27,31} When assessed against the 'clinical validity' criterion, most included guidelines were rated as medium quality (n = 8),^{18,19,24,26–30} followed by high quality (n = 5),^{17,20,21,23,25} and low quality (n = 2).^{22,31} The 'overall quality' of included guidelines was rated as medium for nine guidelines,^{18,19,21,24,26–30} high for four guidelines,^{17,20,23,25} and low for two guidelines.^{22,31}

Scores for the last two criteria, "recommending the guideline" and "utilizing the guideline," were similarly rated (Table 3). Reviewers strongly agreed/agreed that they would recommend/utilize five of the guidelines (scores between 5 and 7),^{17,20,21,23,25} and strongly disagreed/disagreed to recommend/utilize seven guidelines (scores between 1 and 3).^{19,22,24,27,28,30,31} Reviewers were uncertain about recommending/utilizing three of the guidelines (score of 4).^{18,21,26,29}

Biological domain

All 15 included guidelines reported recommendations aligning with the biological domain of the biopsychosocial approach (Table 2; Table S1). These recommendations were broadly categorized as non-pharmacological (eg, exercise; manual therapies, surgery), and pharmacological interventions (eg, non-steroidal anti-inflammatory drugs; opioids), with all but two guidelines^{19,26} reporting recommendations for both categories. The depth of content on the biological domain was rated as moderate (2-stars) in nine guidelines, and high (3-stars) in six guidelines, meaning that the majority of guidelines provided at least a brief discussion of the domain to support the recommendations.

With the exception of five guidelines, ^{20,24,29–31} all guidelines explicitly recommended a multidisciplinary/ multimodal approach to the management of CLBP (Table 2; Table S1). The 15 included guidelines recommended a total of 27 distinct non-pharmacological interventions under the biological domain. Of these, only two interventions were consistently reported in at least 50% (8/15) of included guidelines. These interventions included therapeutic exercise (recommended in 93% of guidelines) and spinal manipulation (67%).

Fourteen distinct pharmacological interventions were recommended across the 15 included guidelines. Only two of these interventions were reported in at least 50% (8/15) of included guidelines. These pharmacological interventions included non-steroidal anti-inflammatory drugs (recommended in 73% of guidelines) and shortterm opioids (53%).

Psychological domain

Recommendations aligning with the psychological domain of the biopsychosocial approach were reported in 13 (87%) included guidelines (Table 2; Table S1). These

			Depth of content"	ntent ^a		
Author (year)	Country of origin	Endorsement agency	Biological focus ^c	Psychological focus ^d	Social focus ^e	Coverage of biopsychosocial domains ^b
Bailly et al. (2021) ¹⁷	France	French National Authority for Health	**	*	**	100%
Bussières et al. (2018) ²⁶	Canada	Cross-institutional collaboration (including McGill University, University of Quebec, World Federation of Chiropractic, Canadian Memorial Chiropractic College, University of Guelph, St. Michael's Hospital, University of Manitoba, & Rush University)	*	*	I	67%
Chenot et al. (2017) ¹⁸	Germany	Cross-organisational collaboration (involving 29 German medical societies and organisations)	**	*	*	100%
Chou et al. (2018) ²⁷	Global	Global Spine Care Initiative	**	*	I	67%
Department of Veterans Affairs & Department of Defence (2022) ²¹	USA	U.S. Department of Veterans Affairs, & U.S. Department of Defence	* * *	***	*	100%
Dupuis and Duff (2019) ³¹	Canada	University of Manitoba	**	I	I	33%
Globe et al. (2016) ¹⁹	USA	Cross-institutional collaboration (Global Health Economics, University of Western States, & Logan University)	*	*	*	100%
Hong et al. (2017) ²⁸	Korea	Korean Society of Spine Surgery	**	**	I	67%
Korownyk et al. (2022) ²⁹	Canada	Cross-institutional collaboration (involving 14 Canadian universities and agencies)	**	**	I	67%
National Institute for Health & Care Excellence (NICE) (2016) ²⁰	UK	National Institute for Health and Care Excellence (NICE)	***	**	*	100%
Parfenov et al. (2019) ²²	Russia	Ministry of Health, Moscow Healthcare Department, Russian Academy of Sciences, Petrovsky Russian Research Center of Surgery, & V.A. Nasonova Research Institute of Rheumatology	* *	* * *	*	100%
Qaseem et al. (2017) ²⁵	NSA	American College of Physicians	**	**	I	67%
Sayed et al. (2022) ³⁰	USA	American Society of Pain and Neuroscience	***	I	I	33%
Shirado et al. (2022) ²⁴	Japan	Japanese Orthopaedic Association	***	***	*	100%
van Wambeke et al. (2020) ²³	Belgium	Belgian Health Care Knowledge Centre	***	**	**	100%

^bProportion of the three domains that were clearly presented within the guideline to any level of detail.

Frocus on age; biomechanics; comorbidity; gender; genetics; metabolic factors; neurochemistry; pathophysiology; physical disability; or severity of disease.

^d Pocus on addictions; attitudes/beliefs; cognitive factors; developmental issues; expectations; literacy/health literacy/nealth literacy; mental illness; past experiences; personality; preferences; psychological stress; readiness to change; selfefficacy; or self-esteem.

Focus on economic factors; employment/occupation; environment/geography; ethnicity/culture/race; family/social support and relationships, health provider/system factors; housing; or language proficiency.

Extent to which management recommendation of CLBP clinical guidelines address each domain of the biopsychosocial approach (n = 15).

TABLE 2

Author (year)	Overall quality of guideline development method (process of development)	Overall quality of guideline presentation (presentation style)	Completeness of reporting	Overall quality of guideline recommendations (clinical validity)	Overall quality of this guideline	I would recommend this guideline for use in practice	I would make use of a guideline of this quality in my professional decisions
Bailly et al. (2021) ¹⁷	5	6	6	6	6	5	5
Bussières et al. (2018) ²⁶	5	2	4	5	4	4	4
Chenot et al. (2017) ¹⁸	7	4	5	5	5	4	4
Chou et al. (2018) ²⁷	3	3	2	3	3	1	1
DVA & DoD (2022) ²¹	9	5	5	9	5	5	5
Dupuis and Duff (2019) ³¹	1	1	1	1	1	1	1
Globe et al. (2016) ¹⁹	5	3	5	4	4	2	2
Hong et al. (2017) ²⁸	4	3	3	З	3	2	2
Korownyk et al. (2022) ²⁹	4	4	4	5	4	4	4
NICE (2021) ²⁰	7	9	7	7	7	9	9
Parfenov et al. (2019) ²²	1	2	1	1	1	1	1
Qaseem et al. (2017) ²⁵	5	6	7	9	6	9	9
Sayed et al. (2022) ³⁰	4	5	4	4	4	3	3
Shirado et al. (2022) ²⁴	4	3	5	5	4	3	3
Van Wambeke et al. (2020) ²³	L	L	L	7	7	7	7
Abbreviations: DoD, Departmer	Abbreviations: DoD, Department of Defence; DVA, Department of Veterans Affairs.	Veterans Affairs.					

TABLE 3 Quality appraisal of included clinical guidelines^{*} (n = 15).

^aAssessed using the 7-item Appraisal of Guidelines for Research and Evaluation Global Rating Scale (AGREE GRS). Scoring: First five items receive a score ranging from 1(lowest quality) to 7 (highest quality); last two items receive a score ranging from 1 (strongly disagree) to 7 (strongly agree).

recommendations referred to both non-pharmacological interventions (13 guidelines; eg, cognitive behavioral therapy) and pharmacological interventions (three guidelines; eg, antidepressant medication). The depth of content on the psychological domain was rated as low (1 star) in five guidelines, moderate (2 stars) in five guidelines, and high (3 stars) in three guidelines.

Guidelines reporting recommendations addressing the psychological domain referred to nine distinct nonpharmacological interventions (eg, progressive muscle relaxation), eight practice considerations (eg, consider patient health beliefs), and two pharmacological interventions (eg, antidepressant medication). Among these 19 distinct recommendations, only two interventions were reported in at least 50% (8/15) of included guidelines. These interventions included patient education (recommended in 60% of 15 guidelines) and cognitive behavioral therapy (60%).

Social domain

Eight (53%) guidelines reported recommendations aligning with the social domain of the biopsychosocial approach (Table 2; Table S1). The depth of content related to the social domain was rated as low (1 star) in six guidelines, and moderate (2 stars) in two guidelines, meaning that no guidelines provided a detailed discussion of the social domain.

The seven guidelines recommended a total of five distinct social interventions, of which no single intervention was reported in more than two guidelines. The social recommendations were also largely ambiguous, with phrases such as "social worker," "promoting return to work" and "ergonomic recommendations."

DISCUSSION

This rapid review examined for the first time, the extent to which clinical guideline recommendations for managing CLBP addressed domains of the biopsychosocial approach. The findings indicated that recommendations addressing the biological domain are well represented and described in current CLBP clinical guidelines. While the psychological domain was also well represented, current guidelines generally do not provide a detailed discussion of this domain. By contrast, the social domain was represented in just over one-half of guidelines, and was principally described in limited detail. This review also identified a degree of diversity and inconsistency with recommendations across all included guidelines.

The predominant biological focus of current CLBP clinical guidelines may, to some extent, reflect the unclear etiology of CLBP; it may also indicate a misguided notion that CLBP is simply a physical symptom rather

than "a dynamic interaction between social, psychological, and biological factors that can both predispose to and result from injury."³² Indeed, managing pain alone is unlikely to address the complex needs of patients with CLBP, and consequently may not be conducive to delivering patient-centered care¹³ and optimal patient outcomes. This claim is supported by evidence from several studies indicating that patients seek care for CLBP not only for pain relief, but also to address psychosocial needs (eg, reduced activity, mood, and quality of life).^{13,33} If the primary purpose of clinical guidelines is to influence clinical decision making,³⁴ then it could be argued that current CLBP guidelines perpetuate unmet health care needs in people living with CLBP by failing to adequately address psychosocial needs, which in turn, can contribute to reduced satisfaction with care.^{13,27}

The modest focus on the psychological domain, and limited attention afforded to the social domain in current CLBP clinical guidelines, is incongruent with the current state of the art. For instance, there is a growing body of evidence demonstrating the effectiveness of various psychosocial interventions in improving outcomes in patients with CLBP, such as cognitive behavioral therapy, counseling, meditation, mindfulness-based stress reduction, pain education, yoga, and social support interventions.^{35–39} There is also mounting evidence supporting a dual relationship between psychosocial factors and CLBP,^{8,40–42} which many CLBP clinical guidelines seem to overlook. Hence, it would be reasonable to conclude that few clinical guidelines foster the provision of a multidisciplinary biopsychosocial approach to CLBP management.

While the paucity of psychosocial guidance in CLBP clinical guidelines is not entirely certain, our appraisal of these guidelines suggests that methodological factors could be partly responsible. For example, the "process of development" for most guidelines was considered to be medium quality, with many guidelines receiving downgraded ratings due to the lack of involvement of all appropriate stakeholders (including psychologists, social workers, patients), during guideline development. Thus, it is proposed that the quality of CLBP clinical guidelines, and the ability of these guidelines to foster a patient-centered biopsychosocial approach to care, could be improved through more diverse stakeholder input in CLBP guideline development.

The composition of guideline development groups can also influence the consistency of guideline recommendations⁴⁴—which was a notable observation of this review; with guideline recommendations both across and within biopsychosocial domains shown to be inconsistent. These inconsistencies can arise when guideline development groups lack representation from pertinent disciplinary experts, allowing conflicts of interest to influence the formulation of recommendations.⁴⁵ Indeed, it is interesting to note that the three guidelines developed for specific disciplinary groups (eg, physicians, surgeons, and chiropractors)^{25,26,28} failed to provide recommendations across all domains of the bio-psychosocial approach.

The quality of included guidelines also may have contributed to inconsistent recommendations across guidelines, with most guidelines considered to be of moderate quality. The methodological/reporting limitations of these guidelines, and the likely impact on the consistency of recommendations, could have adverse implications for clinical practice (eg, clinician trust in and utility of guidelines), patient outcomes, and cost of care.⁴⁶ As such, it is imperative that developers of future CLBP clinical guidelines adhere to independent guideline development standards (eg, WHO)⁴⁷ to ensure guidelines are transparent, reliable, trustworthy, and robust, and are able to positively influence clinician behavior and patient outcomes.

The findings of this rapid review indicate that despite the widespread recognition for, and the importance of a biopsychosocial approach to the management of CLBP, current guidelines do not reflect this. The continued overreliance on the biological domain, with marginal focus on the psychological and social domains, may result in persistent evidence-practice gaps in the management of CLBP. Addressing such gaps will require development of contemporary guidelines that equally value, and provide actionable, consistent recommendations, which span across the biopsychosocial domains. Guidelines that bring together the biopsychosocial domains can facilitate the development and implementation of a multidisciplinary, integrative approach to managing CLBP, which would better align with the current evidence base.

Although this review was novel, and did adhere to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement,⁴⁸ there were some limitations. The review excluded guidelines not published in English, which if included, could have potentially altered the conclusions of the review; notwithstanding, 6 of the 15 guidelines included in this review did originate from non-English speaking countries (eg, Korea, Belgium, Japan). While the review team searched for guidelines across a range of gray literature, there were few included guidelines from clinical institutions (eg, hospitals, primary care settings), largely because such guidelines were not publicly accessible. It is possible that these omitted guidelines may have addressed domains of the biopsychosocial approach differently than included guidelines; thus, the findings of this review may not necessarily apply to such guidelines.

CONCLUSIONS

While the best available evidence supports a multidisciplinary biopsychosocial approach to CLBP management, most clinical guidelines fail to provide adequate guidance to facilitate implementation of such an approach. The CLBP clinical guidelines included in this review provided detailed guidance on the biological domain, yet limited attention and detail were afforded to the psychological and social domains. Inconsistencies in the recommendations reported in these guidelines were also evident. In light of these findings, there is a clear need to improve the transparency, reliability, trustworthiness, and robustness of CLBP clinical guidelines. The inclusion of diverse multidisciplinary stakeholders in guideline development teams, and closer adherence to independent guideline development standards, are pivotal to improving the quality of future CLBP guidelines, and fostering the provision of a biopsychosocial approach to CLBP management.

AUTHOR CONTRIBUTIONS

Matthew Leach was involved in conceptualization, funding acquisition, methodology, project administration, data curation, formal analysis, supervision, writing original draft preparation, and writing—review and editing. Mike Climstein, Gary Fryer, and Saravana Kumar were involved in funding acquisition, methodology, and writing—review and editing. Tamara Agnew was involved in data curation, formal analysis, writing—original draft preparation, and writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors have no competing interests to declare.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and its Supporting Information.

PATIENT CONSENT STATEMENT Not applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Table S1.

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