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REVIEW

Critical Appraisal of Current Acute LBP Management and the Role of a Multimodal Analgesia: A Narrative Review

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ABSTRACT

Acute low back pain (LBP) stands as a leading cause of activity limitation and work absenteeism, and its associated healthcare expenditures are expected to become substantial when acute LBP develops into a chronic and even refractory condition. Therefore, early intervention is crucial to prevent progression to chronic pain, for which the management is particularly challenging and the most effective pharmacological therapy is still controversial. Current guideline treatment recommendations vary and are mostly driven by expertise with opinion differing across different interventions. Thus, it is difficult to formulate evidence-based guidance when the relatively few randomized clinical trials have explored the diagnosis and management of LBP while employing different selection criteria, statistical analyses, and outcome measurements. This narrative review aims to provide a critical appraisal of current acute LBP management by discussing the unmet needs and areas of improvement from bench-to-bedside, and proposes multimodal analgesia as the way forward to attain an effective and prolonged pain relief and functional recovery in patients with acute LBP.

Keywords: Low back pain; Guidelines; Gaps; Evidence based; Acute pain; Analgesics; Multimodal analgesia; Fixed dose combination

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Key Summary Points

Why carry out this study?

Acute low back pain (LBP) stands as a leading cause of disability, and its associated healthcare expenditures become substantial when acute LBP develops into a chronic and even refractory condition.

Current guideline treatment recommendations vary and are mostly driven by expertise with opinion differing across different interventions.

It is difficult to formulate evidence-based guidance when the relatively few randomized clinical trials have explored the diagnosis and management of LBP while employing different selection criteria, statistical analyses, and outcome measurements.

What was learned from the study?

Early intervention is crucial to prevent progression of acute to chronic pain, for which management is particularly challenging and the most effective pharmacological therapy is still controversial.

It is paramount to better align practice with the evidence and to place greater efforts to facilitate the implementation of interventions able to ease the patient management burden, both from the physician's and patient's perspective.

Multimodal analgesia stands as the way forward to attain an effective and prolonged pain relief and functional recovery in patients with acute LBP.

INTRODUCTION

Low back pain (LBP) is a widespread musculoskeletal condition [1], and the global burden of disability associated with this condition has been increasing, particularly within the working-age population, with approximately 70% of years lost through disability in working-aged people and among women compared with men [2, 3]. Thus, LBP occurrence is associated with early retirement, work absenteeism, and loss of productivity presenteeism while being at work [4]. In patients with LBP, pain severity and disability are longitudinally associated to health-related quality of life (HRQoL), and healthcare costs [5, 6]. Overall, strategies to mitigate LBP burden are needed, and the recognition that it is one of the most pressing public health priorities is required [6]. Several barriers have hindered an effective acute LBP management so far. First, it is characterized by a complex etiology (mechanical, neurological, and systemic causes) and underlying pain mechanisms (nociceptive, neuropathic). Second, it is associated with a significant degree of heterogeneity and intrinsic variability. Third, a high rate of recurrence has been documented for acute LBP within 1 year after the first acute episode that may evolve in chronic and disabling pain [7, 8], depending on risk factors for chronicity such as obesity, smoking, severe disability, and depression/anxiety [9]. Identifying the source of pain is still challenging for most clinicians, especially in the primary care setting where patients seek first help in most cases [1]. Practitioners are mostly dealing with patients within a biomedical framework despite the opportunities provided by the biopsychosocial model of LBP, including the conceptualization of LPB etiology and prognosis, as well as the development and testing of many interventions [10]. Overall, there are substantial evidence-to-practice gaps, and a clear need of promoting a better translation of pain knowledge to clinical practice as recently advocated by IASP with the launch of the 2022 Global Year advocacy campaign [11]. The multifactorial nature of LBP supports a multimodal treatment approach by combining analgesic agents with different modes of action

[12]. Mounting evidence suggests that a multimodal analgesic approach to LBP patients can provide effective and adequate pain control, along with a greater improvement of patients' satisfaction with therapy [13]. This narrative review aims to provide a critical appraisal of current acute LBP management by discussing the unmet needs and areas of improvement from bench-to-bedside, and proposes multimodal analgesia as the way forward to attain an effective and prolonged pain relief and functional recovery in patients with acute LBP.

Selection of Evidence

Papers considered for the present narrative review were retrieved via a keyword-based query of multiple databases including PubMed, Google Scholar, and Cochrane library database (e.g., "low-back pain" AND "acute pain" AND "multimodal therapy" AND "multimodal analgesia"), without limitations in terms of publication date. The search was last updated in July 2022 and was limited to papers in English. Papers were selected for inclusion according to their relevance for the topic, as judged by the Authors. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

LBP: WHEN A COMPLEX PATHOPHYSIOLOGY AND A HETEROGENEOUS PATIENT PROFILES HINDER AN APPROPRIATE PATIENT CARE

Acute LBP covers a range of frequently overlapping different types of pain including nociceptive, neuropathic, or nonspecific pain. Vulnerability of the elements encompassing the lumbar spine (e.g., soft tissue, vertebrae, zygapophyseal and sacroiliac joints, intervertebral discs, and neurovascular structures) to different stressors can lead to LBP. Given the low specificity of imaging and diagnostic injections, the diagnosis of this condition continues to be controversial [14]. Clinicians can reliably differentiate acute and persistent mechanical LBP from back pain resulting from a specific cause [15] via a full assessment of key signs and symptoms along with evaluation of red flags. Failure to recognize serious causes early on results in delayed testing and treatment, and may increase patient morbidity and mortality [15]. Red flags can be caused by tumors, infections, fractures, and neurological damage, and if they are present, the patient should be evaluated by the appropriate specialist(s) to get the necessary treatment as part of the overall treatment plan [16] (Table 1). In addition, three categories of acute LBP—the so-called "diagnostic triage"—can be identified, namely, serious spinal pathology, nerve root pain/radicular pain, and nonspecific low back pain [17]. Of note, it is paramount that an accurate diagnosis of pain generators is determined before starting any treatment. Following identification of red flags, excluding the possibility of neuropathic LBP is often the first step in clinical practice.

Clinicians managing patients with LBP often encounter difficulty in differentiating between nociceptive/mechanical and neuropathic pain and selecting the most appropriate pain management strategies, that is, those directed at peripheral and central processes. Such diagnostic uncertainty is associated with limited response to treatment and poor patient outcomes, including unnecessary suffering [18]. The variable LBP disease course and the limited knowledge of pain and disability trajectories also contribute to the currently inadequate provision of LBP care.

It has been increasingly understood that patients with LBP are not experiencing episodes of unrelated occurrences, but rather are suffering from a long-lived condition with a fluctuating course with a trajectory of ongoing or fluctuating pain of low-to-moderate intensity [19, 20]. Importantly, few patients may quickly get well while others may suffer from persistent, severe acute LBP, experience a recurrence within 12 months after recovery, and easily progress to chronic LBP when presenting comorbidities, mental health issues, and poor general health [8, 21, 22]. The most frequent factors promoting recurrence and chronicity in LBP have been investigated by a systematic

Table 1 Red flags for common and nonspecific acute LBP. Elaborated from [18, 54]

Red flags unrelated to specific disease	Red flags endorsed for specific disease
Age of onset less than 20 years or more than 55 years	*Malignancy*
Recent history of violent trauma	History of malignancies/cancer
Constant progressive, nonmechanical pain (no relief with bed rest)	Unexplained/unintentional weight loss
Thoracic (or abdominal) pain	Pain
Past medical history of malignant tumor and of major/significant trauma	Age over 50 years
Prolonged use of corticosteroids	*Fracture*
Drug abuse, immunosuppression, human immunodeficiency virus	History of major/significant trauma
Systemically unwell	Systemic use of steroids
Unexplained/ unintentional weight loss	*Infection*
Widespread sensory deficit (in lower limbs)	Fever $\geq$ 38 °C
Fever $\geq$ 38 °C	Use of corticosteroids or immunosuppressant therapy
	Cauda equina syndrome
	Bladder dysfunction
	Sphincter disturbance

review and encompass a history of LBP (at least more than two previous episodes), low level of job satisfaction, awkward posture, and longer time sitting [23]. Once chronic, LBP is particularly problematic to manage; thus, preventing the transition from acute to chronic LBP is important. It has been reported that between 2% and 48% of patients with acute LBP in primary care settings transition to chronic LBP; of note, these data are in line with a reported overall 32% transition rate to chronic LBP at 6 months [9, 24]. Accordingly, the prevention of progression to chronic pattern of pain is also a pressing issue in LBP management. Increased risk of chronic pain has been associated with a history of compensation for a spinal condition, receipt of work-related sickness payments, or litigation about compensation [25]. However, very recent evidence from a systematic review identified as the most frequently observed risk factors for chronic LBP greater pain intensity, obese status, difficult working positions, and depression. Finally, general anxiety, smoking, and mainly physical work can act as predictors of chronicity [26]. Although attaining a full recovery after LBP can be an ambitious goal, advances in our understanding of the predictors of lack of recovery (such as levels of baseline pain intensity, pain catastrophizing, and depressive symptoms) from acute LBP may inform therapeutic decisions [27]. Finally, from a clinical standpoint, it has been documented that although trajectories of pain and disability may develop in parallel, their psychological predictors may differ. For example, if eradicating pain is not achievable, addressing the psychosocial barriers underlying the development and maintenance of disability may be a goal in pain rehabilitation [27].

LBP PRACTICE GUIDELINES: CURRENT GAPS, LIMITATIONS, AND AREAS OF IMPROVEMENT

To optimize clinical practice and sustainable access to healthcare resources, reducing variability of care and implementing evidence-

based diagnostic and therapeutic approaches are paramount. To this end, clinical practice guidelines (CPGs) can act as a pillar in the promotion of an improved LBP quality of care [28–30]. In 1987, the Quebec Task Force issued the first LBP CPG [31]. Since then, several multidisciplinary LBP guidelines, mostly created by an expert panel through consensus, have emerged, as well as a wide range of treatment options for back pain and ever-growing published evidence [32]. Such an overwhelming volume of evidence, often conflicting and of variable quality (Table 2), is currently hindering the implementation of guideline' recommendations in routine settings. As a result, adherence to guideline-recommended treatments is largely variable [33–35] and more than one in five patients with LBP receive inadequate LBP care [36]. Accordingly, modest patient treatment satisfaction has emerged [37], with even insufficient provision of care being reported in patients with comorbidities [38]. Furthermore, if the scope of acute LBP guidelines would have been the prevention of chronic pain development and of the persistence of LBP-associated disability, recent data underscore current guidelines' failure to meet such important goals, as more than one in five adults in the USA experiences chronic pain, with about 20.5 million (40.9%) reported being bothered "a lot" by back pain [39]. Globally, the years lived with disability (YLDs) of LBP were found to have increased by 52.7% from 1990 to 2017, with Western Europe displaying the greatest value of LBP YLDs [3].

Concerns on methodological limitations affecting the quality of guidelines have been previously raised, with early CPGs appraisals suggesting a generally poor quality of LBP CPGs, even though recently improved, and their limited applicability [40, 41]. Analyzing major LBP guidelines [42–45], several issues emerged, including uncertain value of the available interventions for LBP, inconsistency in clinical efficacy of the tested pharmacological approaches, and a wide variability in the range of pharmacological and interventional options recommended across guidelines. The latter issue may stem from the observation that guideline recommendations are driven by expertise in which opinions differ across different interventions [32]. A critical appraisal of the most recent CPGs for LBP interventions by means of the Appraisal of Guidelines Research and Evaluation (AGREE) II instrument, the gold standard for critical appraisal of guidelines, has been published recently [46]. Methodological limitations influencing the quality of CPGs were emphasized, including a very limited participation of patients and their advocates. Similarly, a very recent appraisal confirmed that CPGs varied in quality, with most being characterized by the lowest score in stakeholder involvement, rigor of development, and applicability [47].

To advance LBP patient care and support clinicians in management decisions, an evidence-based guidance is of utmost relevance. However, CGP recommendations have favored management approaches such as the "wait and see" approach that appears inadequate to effectively tackle the LBP burden as it is built on the erroneous assumption that most people with acute LBP will get well without any issue [7, 48]. Surprisingly, most guidelines (10 out of 14; 71%) for the management of nonspecific LBP in primary care recommend reassuring the patient that LBP is not a serious illness and that it may have a favorable prognosis (Table 2) [49, 50]. Current CPGs have supported, so far, the erroneous concept of "an expected course of LBP" that basically ignores the natural history of LBP and the well-documented trajectories of pain and disability. Although this stepped care approach seems promising given the shortage of resources available in most healthcare systems, a delayed intervention is particularly detrimental in patients at high risk of chronicity or in those suffering from comorbidities such as depression, which is a well-known correlate of chronic pain [51]. Of note, postponing adequate treatment may promote rather than prevent the transition from acute into subacute and chronic LBP [48].

Diagnostic workup with red flags and therapy recommendations for patients with LBP also vary across CPGs [52]. Although different red flags are present in LBP guidelines, there is no consensus between guidelines for which red flags to endorse and a marked variability in precise definitions of the red flags (e.g.,

Table 2 Overview of clinical practice guidelines for acute LBP management. Elaborated from [35, 45, 46, 52, 53]

Clinical guideline	Aim of the guideline	Clinical premise	Recommended intervention for acute LBP	Areas of inconclusive evidence	Ref
A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society (2007)	To present the available evidence for evaluation and management of acute and chronic LBP in primary care settings	Clinicians should inform all patients of the generally favorable prognosis of acute LBP with or without sciatica, including a high likelihood for substantial improvement in the first month	Clinicians should provide patients with evidence-based information on LBP regarding their expected course, advise patients to remain active, and provide information about effective self-care options. Clinicians should consider the use of medications with proven benefits in conjunction with back care information and self-care. For most patients, first-line medication options are paracetamol or nonsteroidal antiinflammatory drugs (NSAIDs)	There is insufficient evidence to guide specific recommendations on the timing of or indications for referral, and expertise in management of LBP varies substantially among clinicians from different disciplines (including primary care providers)	Chou et al. Ann Intern Med. 2007;147:478–491

Table 2 continued

Clinical guideline	Aim of the guideline	Clinical premise	Recommended intervention for acute LBP	Areas of inconclusive evidence	Ref
Canadian practice guideline on primary care management of LBP (2015)	To increase the use of evidence-informed conservative approaches to the prevention, assessment, diagnosis, and treatment in primary care patients with LBP; to promote appropriate specialist referrals and use of diagnostic tests in patients with LBP; to encourage patients to engage in appropriate self-care activities	Practitioners should emphasize that acute low back pain is nearly always benign and generally resolves within 1–6 weeks. Physicians are encouraged to reinforce that pain typically resolves in a few weeks without intervention	Superficial heat (application of heating pads or heated blankets) is recommended for the short-term relief of acute LBP. Prescribe medication, if necessary, for pain relief preferably to be taken at regular intervals. First choice paracetamol, second choice NSAIDs	Inconsistencies are found in the recommendation regarding herbal treatments Despite the publication demonstrating no benefit of paracetamol over placebo for LBP in primary care [56], paracetamol is recommended in acute and chronic LBP. Canadian guidelines advocate the use of tricyclic antidepressants (TCAs) and paracetamol. For many of these, the evidence base is either limited or not promising. Finally, Canadian guidelines offer detail on suggested care pathways, though these are largely determined by expertise rather than evidence	

Table 2 continued

Clinical guideline	Aim of the guideline	Clinical premise	Recommended intervention for acute LBP	Areas of inconclusive evidence	Ref
NICE Guideline on Low Back Pain and Sciatica NG59 (2016)	To improve people's quality of life by promoting the most effective forms of care for LBP and sciatica	This guideline advocates education towards an "expected" course of LBP, in which the probability of a rapid improvement in symptoms is high, potentially to reduce the risk of fear/catastrophizing and to moderate expectations	NICE only recommends considering the use of NSAIDs, and if NSAIDs are ineffective, contraindicated, or not tolerated, then consider a weak opioid, with or without paracetamol for acute LBP where an NSAID could not be used	The duration of symptoms was not specified. The recommended combination weak opioid/paracetamol for acute LBP is based on very limited evidence Across all the interventions reviewed by the NICE group, no intervention was considered to have strong enough evidence to warrant a clear "offer" recommendation. NICE guidelines offer detail on suggested care pathways, though these are largely determined by expertise rather than evidence	National Guideline Centre (UK) "Low back pain and sciatica in over 16s"

Table 2 continued

Clinical guideline	Aim of the guideline	Clinical premise	Recommended intervention for acute LBP	Areas of inconclusive evidence	Ref
A Clinical Practice Guideline from the American College of Physicians (2017)	To provide treatment guidance based on the efficacy, comparative effectiveness, and safety of noninvasive pharmacologic and nonpharmacologic treatments for acute (< 4 weeks), subacute (4 to 12 weeks), and chronic (> 12 weeks) LBP in primary care	Most patients with acute LBP improve over time regardless of treatment. Clinicians should inform all patients of the generally favorable prognosis of acute LBP with or without sciatica, including a high likelihood for substantial improvement in the first month	Clinicians and patients should select nonpharmacologic treatment with superficial heat (moderate-quality evidence), massage, acupuncture, or spinal manipulation (low-quality evidence). If pharmacologic treatment is desired, clinicians and patients should select NSAIDs or skeletal muscle relaxants (moderate-quality evidence)	Most RCTs enrolled a mixture of patients with acute, subacute, and chronic LBP, so it is difficult to extrapolate the benefits of treatment compared with its duration. Evidence on patient-important outcomes, such as disability or return to work, is largely unavailable	Qaseem et al. Ann Intern Med. 2017;166:514–530

Table 2 continued

Clinical guideline	Aim of the guideline	Clinical premise	Recommended intervention for acute LBP	Areas of inconclusive evidence	Ref
Clinical practice guidelines for the management of nonspecific low back pain in primary care (2018)	Clinical practice guidelines provide evidence-based recommendations to assist decision-making about health interventions	Most guidelines recommend reassuring the patient that LBP is not a serious illness regardless of the duration of symptoms or reassuring patients with acute LBP of the favorable prognosis	Most guidelines recommend advice to maintain normal activities for patients with acute LBP, and some guidelines recommend the same advice for patients with any duration of symptoms	Acute LBP is invariably defined as less than 4, 6, and 12 weeks. Discrepancies in the recommendations for the use of paracetamol, muscle relaxants, and herbal medicines. Most guidelines recommend the use of weak opioids for short periods if NSAIDs are contraindicated or not effective for patients with acute LBP, despite an absence of relevant clinical trials	Oliveira et al. European Spine Journal 2018; 27:2791–2803

"trauma," "severe trauma," "major trauma"). Overall, a core set of red flags ideally endorsed by all guidelines is largely awaited [52].

Although the use of nonsteroidal antiinflammatory drugs (NSAIDs) for patients with acute and chronic LBP is recommended while considering the risk of adverse events (e.g., renal, cardiovascular, and gastrointestinal), one in two CPGs still recommend in favor of paracetamol, despite no benefit of paracetamol over placebo for LBP in primary care being reported so far [32, 53]. Moreover, most guidelines recommend the use of weak opioids for short periods if NSAIDs are contraindicated or not effective for patients with acute LBP, despite an absence of relevant clinical trials and the potential increased harms for patients with nonspecific LBP [49].

Overall, there is a glaring demand for additional high-quality clinical evidence, possibly built upon a rigorous clinical trial design, an evidence-based medication choice, and broader inclusion criteria acknowledging both the heterogeneity and variability of LBP. In addition, clinical trials should also include, among the measured endpoints, not only the differences in pain intensity but also variation in pain severity, pain-related distress, and interference in daily activities, as well as improvement in functional disability [54, 55]. Meaningful tools such as the Roland–Morris Disability Questionnaire (RMDQ) can be of help in clinical settings, particularly in the follow-up period, to evaluate patients' response and restoration of well-being. To this end, clinical trials should investigate how to increase the likelihood that patients will achieve outcomes that matter the most for them. Useful insights have been provided by the identification of core outcome domains for clinical trials in nonspecific LBP, namely "physical functioning," "pain intensity," "health-related quality of life,"and "number of deaths" [56]. Furthermore, it is desirable to gather evidence from head-to-head comparisons of newly marketed drugs with well-established treatment options. Such findings may help identifying first-line combination pharmacotherapy to guide through a rational approach in medical treatment of patients with LBP. This would finally create evidence-based guidelines rather than consensus-based guidelines, and potentially make it easier to implement in clinical routine settings [57]. Table 3 illustrates the gaps, limitations, and areas of improvement of currently available LBP CPGs.

THE ROLE OF MULTIMODAL THERAPY IN LBP MANAGEMENT

Multimodal therapy approaches are emerging as promising strategies to enhance clinical outcomes for patients with several diseases, including diabetes [58], obesity [59], rheumatic diseases [60], cancer [61], thrombotic diseases [62], and pain [13]. Regarding the latter, the objectives of multimodal therapy are to lower pain intensity and drug-related adverse events, to speed up recovery, and to facilitate rehabilitation. Ideally, multimodal therapy should restore patients' functionality, ameliorate QoL, and prevent progression of acute to chronic pain [63]. The biopsychosocial model acknowledges that LBP derives from a dynamic crosstalk between social, psychological, and biological factors that can both predispose to and result from injury [64]; therefore, these factors should be taken into account when an interdisciplinary treatment plan is designed [14]. As the factors affecting the intensity and duration of acute LBP vary significantly, multimodal therapy stands as the most logical approach [48]. Therefore, pain relief can be achievable by targeting different sites of the nociceptive pathway and by managing the plethora of pain-related conditions, as well as pain correlates (*e.g.*, depression, sleep abnormalities) through pharmacologic and nonpharmacologic modalities.

In one study, multimodal therapy (4 h per day for 20 days, consisting of medical training therapy, cognitive-behavioral therapy, physiotherapy, and patient education) was evaluated in a primary care setting and offered meaningful reduction in pain intensity, interference with daily living, depressive mood, and QoL [65]. It has also been reported to ease the recovery of physical functioning and subsequently the return to work-related activities [66]. The effectiveness of an inpatient follow-up

Table 3 Current gaps and areas of improvement in acute LBP management clinical practice guidelines. Elaborated from data in [3, 10, 35, 43, 49, 51]

Current CPS gaps	Areas of improvement
CPGs are mostly consensus-based rather than evidence-based	Build high-quality clinical evidence upon a rigorous clinical trial design and evidence-based medication choice
CPGs are based on the assumption that LBP is short lived, benign, and effectively addressed by a stepped care approach	Gather evidence from studies exploring both pain and disability trajectories in patients with LBP, as well as identifying the factors predicting recurrence and chronicity
CPGs are characterized by a limited applicability and implementation in routine settings and a wide variability in the recommended pharmacological and interventional options	Gather evidence from head-to-head comparisons of newly released drugs with older agents to improve appropriateness of pharmacotherapy in clinical practice
CPGs provide conflicting evidence and of variable quality, and acknowledge limited participation of patients and their advocates	Design high-quality clinical evidence that investigate how to increase patients biopsychosocial benefits, submitting them to active questionnaires

CPG clinical practice guideline, *LBP* low back pain

after multimodal therapy in 155 patients with chronic LBP has also been evaluated [67]. Multimodal therapy improvement in terms of pain intensity, depression, anxiety, and well-being were significant after a 3-month follow-up. Of note, patients seemed to benefit more from attending multimodal therapy in an earlier stage of healthcare [68]. These findings further support the notion that early intervention is important in patients with acute LBP to prevent progression to chronic pain [69, 70].

Finally, providing high value care in LBP should mean placing greater attention on patient-reported outcomes and acknowledging the impact of patient satisfaction on treatment outcomes. It has been suggested that multimodal therapy aims to increase patient satisfaction in patients with acutely exacerbated chronic pain [71, 72]. A retrospective analysis evaluating multimodal treatment in 375 patients with chronic pain-related rheumatic diseases (111 of which reported LBP) supported this data [60]. Of note, after implementing multimodal therapy, a significant improvement of mental (mood) status was observed despite high levels of pain reported on admission in the study population; this improvement was also described in patients with LBP [60].

One key component of multimodal therapy is pharmacological treatment that is mostly geared toward analgesia and symptom management. Pharmacological treatments for the management of patients with LBP generally encompass paracetamol and NSAIDs as first-line treatment options, along with opioids, tricyclic antidepressants (TCAs), and anticonvulsants, the use of which depends on the type of LBP and patient history [38, 73]. However, evidence supporting the efficacy of paracetamol [53, 74] is insufficient for drawing firm conclusions, as acetaminophen was found not effective in reducing acute LBP [75] nor able to affect the time of recovery compared with placebo on a regular or as-needed dosing regimen [53]. In addition, no difference between paracetamol and placebo was documented in pain and disability at 1 week (immediate term); 2, 4, and 12 weeks (short term); or on QoL, function, global impression of recovery, and sleep quality [76]. Finally, conflicting results about the use of several NSAIDs in LBP have been reported [77]. Nevertheless, a patient-centered approach, acknowledging the patient's other

comorbidities, medications, and previously trialed treatments should guide treatment decisions.

Along with therapeutic interventions, interventional pain management modalities could be a useful component in multimodal treatment of LBP [70]. The most common include epidural steroid injections (ESI), radiofrequency ablation (RFA) of facet or sacroiliac joint innervation, intradiscal and vertebral augmentation procedures, and intrathecal drug delivery with implantable pump [78, 79]. Although ESI can be of help for short-term management of subacute/chronic LBP, no long-term effect on pain or surgical rates have been documented. Nevertheless, ESIs may often be used as a panacea for LBP, despite data showing that they are most effective for specific structural etiologies [80]. In patients who experienced the failure of other pain therapies, the use of implantable drug-delivery systems was associated with disability reduction and significant improvement of QoL and patient satisfaction with this therapy [81]. Overall, considering both the improvement of pain intensity in at least the short and medium terms, and the equivocal results in terms of functional improvement [79], further studies are required to fully support interventional pain procedures' role in LBP management [82].

MULTIMODAL ANALGESIA: THE WAY FORWARD

It has been suggested that LBP management should address the different patterns of pain trajectories (continuous pain along with acute flares) that characterize it [83], acting on the multiple pain generator mechanisms (either mechanical or neuropathic) to lower the risk of recurrence and, consequently, that of chronicity [38]. A recent Delphi study suggested that physicians would favor multidisciplinary-multimodal approaches to achieve the objectives of LBP management, thereby shifting towards treating LBP as a biopsychosocial issue that requires management in-kind [38]. Compared with monomodal analgesia, multimodal analgesia offers several advantages including greater analgesia, shorter hospitalization times, and improved recovery and function in postoperative and osteoarthritis [84]. Therefore, multimodal analgesia has been included in the current international guideline recommendations for both postoperative and osteoarthritis pain [85, 86].

When two or more analgesic medications are combined (either in free or fixed formulations) for pain relief, it allows for lower doses of each drug to be administered, thus limiting the risk of adverse drug effects with the maximum benefit. Of note, advantages of fixed-dose combination (FDC) products that may ease the patients' management burden, include dosing convenience, reduction of pill burden, the potential for greater patient adherence, and, in the case of FDC products involving an opioid and a nonopioid agent, opioid-sparing effects and fewer side effects due to the reduced doses of each single substance [87]. Over time, multimodal analgesia has become more standard to manage pain as effectively as possible, also reducing opioid exposure [88] without sacrificing patient comfort or impeding rehabilitation [89]. This is relevant if one considers that opioids remain a common drug of choice for acute LBP in the emergency department (ED) [90] and their use in ED has been associated with an increased length of stay [91]. Another reported advantage of multimodal analgesia is the possible reduction in acute pain transition to chronic pain [92]. Such approach should be preferred in patients suffering from acute LBP whose risk of chronicity is worrisome and hinders patient functional recovery, thus further impairing patients' QoL.

While waiting for novel agents, a major aim in current pain research is to use the existing drugs in a better way. Therefore, an effective analgesic FDC can be developed by combining a COX inhibitor with an opioid, whose clinical efficacy and tolerability profiles have been well documented. Therefore, clinicians should be aware that not all COX inhibitors are equally valuable as component of multimodal analgesia or equally as effective at providing the antiinflammatory and analgesic benefits with less untoward effects, mostly gastrointestinal (GI) and cardiovascular (CV). As per GI and CV toxicity, NSAIDs differ in terms of opioid-

sparing effect [93]. Among NSAIDs, dexketoprofen provides a significant reduction in opioid use (36–50%), which is much greater than that attained upon treatment with diclofenac, ketorolac, and ibuprofen [93]. Celecoxib, a NSAID that acts primarily via inhibition of cyclooxygenase-2, has recently been combined in the novel co-crystal form of tramadol-celecoxib (CTC) 200 mg BID. As an urgent need for pain therapies to be effective and tolerated, in the context of multimodal analgesia, CTC has been developed for the management of acute moderate-to-severe pain. Unfortunately, in the latest randomized, double-blind, phase 3 STARDOM2 trial—in acute moderate-to–severe pain after abdominal hysterectomy—CTC was not superior to tramadol alone, failing to meet the primary endpoint [94].

Importantly, opioids also differ in terms of cardio–pulmonary tolerability, GI discomfort, and somnolence. Tramadol offers an alternative to other opioids as its two complementary synergistic actions, i.e., agonism to opioid receptor and inhibition of serotonin and norepinephrine re-uptake, enhance its pain relief effects and improve its tolerability profile. Unlike other weak opioids, tramadol has no relevant effects on CV and pulmonary parameters, and its administration is associated with less constipation and opioid-induced bowel dysfunction, along with a low addiction rate [95, 96].

Combinations of oral analgesics including tramadol were investigated with the twice-daily fixed combination of 75 mg tramadol/650 mg paracetamol (DDS-06C) in the treatment of moderate-to-severe acute LBP [97]. Although it did not include an active treatment arm as a comparator, in this study, the superior analgesic efficacy of DDS-06C versus placebo was confirmed for the primary efficacy endpoint. The relatively high response observed in the placebo group is consistent with the well-characterized "placebo response" observed in other pain studies [98, 99].

The fixed dose combination tramadol/dexketoprofen (TRAM/DKP) holds great promise for multimodal pain management. Of note, the rapid onset of analgesic effect of DKP, with its endpoint antiinflammatory activity associated with the sustained (mean duration: 8.1 h) action of TRAM, makes this combination a valuable tool to achieve multimodal analgesia [100–102]. Owing to its central analgesic effect, peripheral analgesic action, and antiinflammatory activity [83], TRAM/DKP may contribute to pain relief in acute exacerbations of LBP [103]. Recent observational studies in LBP patients showed that TRAM/DKP can be a valuable and effective option [104, 105]. However, such studies were single-center retrospective clinical trials with relatively small sample sizes (less than 100 patients each) and excluded patients with history of chronic LBP. As outlined in Table 3, there is a clear need to build high-quality clinical evidence to support effective acute LBP management. To this end, a multicenter, randomized, double-blind, double-dummy parallel group, placebo, and active controlled study (DANTE Study) is currently ongoing to prospectively assess the efficacy of TRAM/DKP in moderate-to-severe acute LBP with or without radiculopathy (EU register EudraCT number: 2019-003,656-37) [106]. Overall, the DANTE study aims to address some of the areas of improvement listed in Table 3, thus providing substantial advancement in the routine management of patients with acute LBP, thereby easing the considerable burden associated with such a disabling condition (Fig. 1).

DISCUSSION

Worldwide, LBP ranks as the leading contributor to disease disability, and a recent World Health Organization (WHO) report has confirmed that LBP is the primary cause of disability in 160 countries [107]. Therefore, early intervention is pivotal in patients with acute LBP to prevent progression to chronic pain. Despite the available acute LBP treatment options, most of them lack a high level of evidence [32, 49, 50]. Current guideline treatment recommendations, being consensus-based, are mostly driven by expertise with opinion differing across different interventions. However, it is difficult to formulate evidence-based guidance when relatively few randomized clinical trials

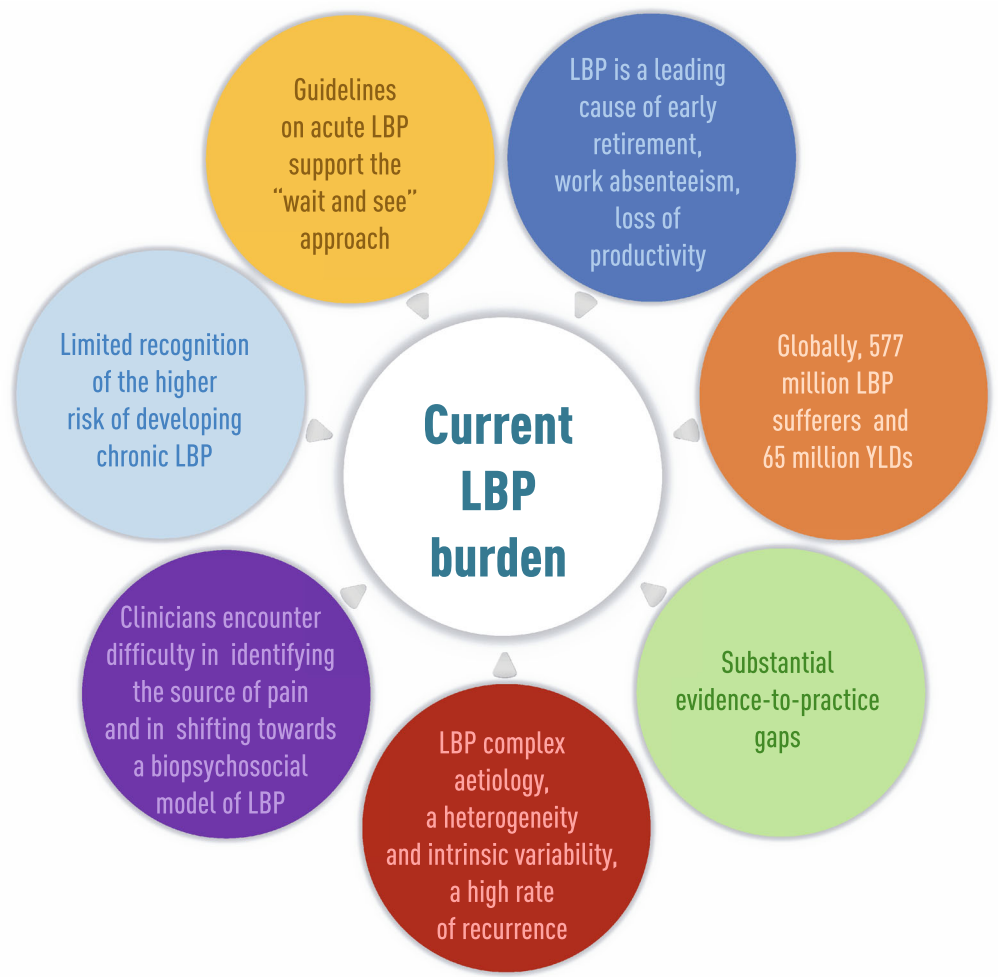

Fig. 1 Current LBP burden. Graphical elaboration of data in [3, 4, 10, 11, 15, 42, 51]. *LBP* low back pain, *YLDs* years lived with disability

have investigated the diagnosis and management of LBP, and these have employed different selection criteria, statistical analyses, and outcome measurements. Therefore, further studies addressing the areas of improvement listed in Table 3 are urgently needed. Also, the existing guidance provided physicians with limited support to identify both the etiology of pain and the underlying pain mechanisms, and subsequently to guarantee the most appropriate therapeutic regimen for the specific patient. Importantly, patient education is recommended in treatment guidelines as a part of a multimodal approach to improve self-efficacy and coping strategies [49, 108]. Therefore, it is imperative for healthcare professionals to involve patients with LBP in the care process and have access to up-to-date, evidence-based information to assist clinicians in treatment decision-making. In this context, physicians' education should be promoted as it is directly related to better patient outcomes, favoring patient responses to physicians' actions, thus leading to reductions in healthcare utilization [109]. Of note, clinicians should shift away more from the biomedical framework alone toward combining it with a biopsychosocial model, being aware of the potential negative implications of addressing only pain severity and ignoring what matters the most for

patients, namely disability, functional impairment, and QoL [64]. Finally, pursuing a value-based care in LBP means working as integrated practice units centered around the patient's clinical condition. Therefore, to increase awareness on the importance of communication among all the specialists the patient encounters along his/her disease journey should be a priority for all the scientific societies engaged in pain management. The words "low back pain" yield almost 44,000 results on PubMed, suggesting ever-expanding understanding of back pain and the associated psychological and social risk factors, as well as genetics factors. However, as recalled by many, this high volume of evidence represents a paradox as it has failed to translate into a clinical practice able to provide patients with LBP with the care they deserve [64, 110]. It is paramount to better align practice with the evidence, and to place greater efforts to facilitate the implementation of interventions able to ease the patient management burden, both from the physician's and patient's perspective. This means working towards a redesign of clinical pathways and patient journey, during which the patient will not face avoidable steps before appropriate care is given. To this end, easy to apply guidelines and practical tools useful in different care settings can be of help.

Our narrative review has provided a critical appraisal of CPGs that can be of help in evaluating strategies to manage pain in this major health issue setting, especially when the HCP could face a possible gap or unmet needs in guidelines. Hopefully, the unmet needs in LBP management highlighted here, and the promising role of multimodal analgesia described, could stimulate researchers to produce new evidence that can help in improving CPGs, with a consequent improvement in LBP management.

CONCLUSIONS

LBP represents one of the most difficult challenges for the healthcare professionals coping with pain patients. From the perspective of healthcare professionals, its epidemiology is difficult to accept. In its acute manifestation it must be treated rapidly and as well as possible, considering that it may become responsible for a transformation of pain from acute to chronic. Notwithstanding that, its incidence and prevalence are increasing, as well as the number of chronic low back pain patients is increasing. Generally, only poor-quality LBP CPGs are currently available, and many therapies have been suggested to physicians. Overall, there is a glaring demand for additional high-quality clinical evidence, possibly built upon a rigorous clinical trial design, with an evidence-based medication choice and broader inclusion criteria acknowledging both the heterogeneity and variability of LBP. A multispecialist and multimodal approach for management is a universally accepted concept. Inside this, multimodal pharmacologic therapy remains a cornerstone for acute LBP treatment. This must be as simple and efficacious as possible. The fixed-dose combinations of NSAIDs and weak opioids seem the most appealing multimodal pharmacological therapies available for these patients. Of these, the combination of dexketoprofen and tramadol, has excellent potential as therapy, already proven as very efficacious in other acute moderate-to-severe pain conditions.

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