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REVIEW ARTICLE

Non-surgical advanced therapies for chronic low back pain in adults: systematic review of randomized controlled trials

Terapias avançadas não cirúrgicas para dor lombar crônica em adultos: revisão sistemática de ensaios clínicos randomizados

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ABSTRACT

BACKGROUND AND OBJECTIVES: Chronic low back pain (CLBP) is a leading cause of disability worldwide, with complex neurobiological and psychosocial mechanisms that often limit the effectiveness of conventional treatments. Recent advances in non-surgical interventions—such as neuromodulation, regenerative therapies, and multimodal physiotherapy—offer promising alternatives for pain modulation and functional recovery. The objective of this study was to systematically review the evidence from randomized controlled trials (RCTs) evaluating the efficacy and safety of advanced non-surgical therapies for CLBP in adults.

CONTENTS: Searches were conducted in Pubmed, Scopus, Web of Science, and ScienceDirect (2015–2025). Eligible studies included RCTs assessing non-surgical interventions such as restorative neurostimulation, spinal cord stimulation, neuromodulation (TENS, rTMS, tDCS, rPMS, taVNS), regenerative biologic injections (PRP, MSCs), and multimodal physiotherapy programs. Primary outcomes were pain intensity and functional disability; secondary outcomes included quality of life and adverse events. Twenty-two RCTs encompassing over 4,000 participants met inclusion criteria. Restorative and spinal cord stimulation demonstrated clinically meaningful pain and disability reductions (up to −19.7 Oswestry Disability Index (ODI) points; ≥60% responder rates). Regenerative therapies with PRP and MSCs achieved long-term improvements lasting up to 36 months with excellent safety profiles. Multimodal physiotherapy programs improved quality of life and function, while non-invasive neuromodulation yielded consistent short-term analgesic benefits. Across studies, adverse events were rare and mild.

CONCLUSION: Advanced non-surgical therapies are effective and safe for managing CLBP, particularly when integrated within multimodal, mechanism-based rehabilitation programs. Combining physiotherapy, neuromodulation, and regenerative approaches may optimize neuroplastic and functional recovery. Further large-scale RCTs with standardized protocols and long-term follow-up are warranted to consolidate these findings.

KEYWORDS: Chronic low back pain, Neuromodulation, Physiotherapy, Platelet-rich plasma, Regenerative therapy, Spinal cord stimulation.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A dor lombar crônica (DLC) é uma das principais causas de incapacidade em todo o mundo, apresentando mecanismos neurobiológicos e psicossociais complexos que frequentemente limitam a eficácia dos tratamentos convencionais. Avanços recentes em intervenções não cirúrgicas oferecem alternativas promissoras para a modulação da dor e a recuperação funcional. O objetivo deste estudo foi revisar sistematicamente as evidências provenientes de ensaios clínicos randomizados (ECRs) que avaliaram a eficácia e a segurança das terapias avançadas não cirúrgicas para o tratamento da DLC em adultos.

CONTEÚDO: As pesquisas foram realizadas no Pubmed, Scopus, Web of Science e ScienceDirect (2015–2025). Foram incluídos ECRs que avaliaram intervenções não cirúrgicas, como neuroestimulação restaurativa, estimulação da medula espinhal, neuromodulação (TENS, rTMS, tDCS, rPMS, taVNS), injeções biológicas regenerativas (PRP, CTMs) e programas multimodais de fisioterapia. Os resultados primários foram a intensidade da dor e a incapacidade funcional; os resultados secundários incluíram a qualidade de vida e os eventos adversos. Vinte e dois ECRs, envolvendo mais de 4.000 participantes, atenderam aos critérios de inclusão. A estimulação restaurativa e a estimulação da medula espinhal demonstraram reduções clinicamente significativas na dor e na incapacidade (até -19,7 pontos no Índice de Incapacidade de Oswestry (ODI); =60% de taxa de resposta). As terapias regenerativas com PRP e CTMs promoveram melhoras duradouras por até 36 meses, com excelente perfil de segurança. Programas multimodais de fisioterapia resultaram em melhora da qualidade de vida e da função, enquanto as técnicas de neuromodulação não invasiva proporcionaram benefícios analgésicos consistentes a curto prazo. Em todos os estudos, os eventos adversos foram raros e leves.

CONCLUSÃO: As terapias avançadas não cirúrgicas são eficazes e seguras para o manejo da DLC, especialmente quando integradas em programas de reabilitação multimodais e baseados em mecanismos fisiopatológicos. A combinação de fisioterapia, neuromodulação e abordagens regenerativas pode otimizar a recuperação neuroplástica e funcional. São necessários mais ECRs de larga escala, com protocolos padronizados e acompanhamento a longo prazo, para consolidar esses resultados.

DESCRITORES: Dor lombar, Estimulação magnética transcraniana, Estimulação transcraniana por corrente contínua, Plasma rico em plaquetas, Medicina regenerative, Estimulação da medula espinal.

HIGHLIGHTS

- Advanced non-surgical therapies, including neuromodulation and regenerative approaches, significantly reduce pain and disability in chronic low back pain (CLBP)
- Multimodal physiotherapy programs improve function, quality of life, and patient engagement by addressing both physical and cognitive-behavioral factors
- Non-invasive neuromodulation methods (rTMS, tDCS, taVNS, TENS) show consistent analgesic effects and enhance neuroplastic adaptation when combined with exercise
- Regenerative biological therapies using platelet-rich plasma and mesenchymal stem cells demonstrate long-term safety and durable clinical benefits up to 36 months

INTRODUCTION

Chronic low back pain (CLBP) remains one of the leading causes of disability worldwide, affecting approximately 619 million people in 2020, with projections suggesting an increase to 843 million by 2050[1]. It is estimated that up to 84% of the global population will experience at least one episode of low back pain during their lifetime, and about 20% of these cases progress to the chronic form, lasting longer than three months[2]. Thus, CLBP represents a condition of substantial global impact that transcends physical discomfort, impairing functionality, productivity, and quality of life. Its etiology is multifactorial, involving complex interactions among biomechanical, neurophysiological, and psychosocial factors that contribute to the persistence of nociceptive and neuropathic components often resistant to conventional therapeutic approaches[3,4].

The pathophysiology of CLBP encompasses alterations in both peripheral and central nociceptive processing mechanisms. Initially, stimuli originating from musculoskeletal structures—such as intervertebral discs, facet joints, and paraspinal muscles—activate nociceptors and trigger the release of inflammatory mediators, including prostaglandins and pro-inflammatory cytokines. This process leads to peripheral sensitization, characterized by a lowered neuronal excitability threshold and an enhanced response to mechanical or thermal stimuli[4,5]. Peripheral sensitization therefore marks the initial stage of CLBP, contributing to its persistence and clinical progression.

With the persistence of nociceptive input, central sensitization develops, characterized by neuronal hyperexcitability within spinal and supraspinal structures such as the dorsal horn of the spinal cord, thalamus, and anterior cingulate cortex[5,6]. This state involves increased glutamatergic activity and reduced GABAergic and serotonergic inhibition, resulting in pain amplification and the perception of pain even in the absence of peripheral stimuli[7,8]. Additionally, cortical alterations in regions involved in emotion and cognition reinforce the multidimensional and neuroplastic nature of CLBP, demonstrating that its manifestation extends beyond the sensory domain and includes affective and cognitive aspects of the pain experience.

CLBP thus constitutes a major public health problem, responsible for high rates of physical disability and work absenteeism worldwide. Its high prevalence is associated with population aging, sedentary behavior, and adverse occupational conditions, generating substantial direct and indirect costs for healthcare systems and society[9]. Beyond functional impairment, chronic pain compromises autonomy and psychosocial well-being, interfering with daily activities and social interactions.

Given this complex pathophysiology and the limitations of traditional therapeutic approaches, there is growing interest in advanced non-surgical therapies capable of modulating pain, restoring function, and promoting neuroplastic adaptation safely and effectively. Among these approaches are multimodal physiotherapy programs, peripheral and central neuromodulation techniques (such as TENS, rTMS, tDCS, and auricular vagus nerve stimulation), and regenerative therapies, including platelet-rich plasma (PRP) and mesenchymal stem cell (MSC) treatments[10-13].

Multimodal physiotherapy programs integrate various strategies, such as strengthening exercises, motor control training, postural reeducation, and cognitive interventions, aiming not only to reduce pain but also to enhance mobility, functionality, and social participation[14,15]. Neuromodulation techniques act on peripheral and central nociceptive circuits, promoting analgesia and facilitating adaptive mechanisms of neural plasticity[16,17]. Regenerative therapies aim to repair degenerated or inflamed spinal structures, with the potential to improve function and provide sustained symptomatic relief[18,19].

Despite significant progress, the heterogeneity of protocols, intervention parameters, and outcome measures still hinders the establishment of optimized strategies. Therefore, systematic reviews synthesizing evidence from randomized clinical trials (RCT) are essential to elucidate the efficacy, safety, and clinical applicability of these therapies, thereby supporting evidence-based physiotherapeutic practice and contributing to more effective management of CLBP.

CONTENTS

This systematic review evaluated the effects of non-surgical advanced therapies on CLBP in adults. The review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[20] guidelines and was prospectively registered in PROSPERO (CRD420251151485).

Eligibility criteria

Eligibility criteria were defined according to the PICO framework:

Population: adults (≥18 years) diagnosed with CLBP (pain duration ≥3 months), including nonspecific, neuropathic, or discogenic etiologies. Studies focusing exclusively on postoperative pain, acute/subacute conditions, or pediatric populations were excluded.

Intervention: non-surgical, advanced therapeutic interventions targeting pain modulation, functional restoration, or biological repair. Eligible interventions included restorative neurostimulation, spinal cord stimulation (SCS), dorsal root ganglion (DRG) stimulation, peripheral or central neuromodulation (e.g., TENS, rTMS, tDCS, rPMS, taVNS), regenerative injections (e.g., platelet-rich plasma [PRP], bone marrow concentrate, mesenchymal stem cells), and structured physiotherapy-based multimodal rehabilitation programs.

Comparison: sham stimulation, placebo injections, usual medical management, conventional physiotherapy, or pharmacological therapy (e.g., NSAIDs, corticosteroids).

Primary outcomes: pain reduction assessed by validated scales such as the Visual Analog Scale (VAS) or Numeric Rating Scale (NRS), and functional disability measured by the Oswestry Disability Index (ODI), Roland-Morris Disability Questionnaire (RMDQ), or Functional Rating Index (FRI).

Secondary outcomes: quality of life (e.g., EQ-5D, SF-36), physical mobility, sleep, or patient-reported global improvement. Studies were also required to report safety or adverse events.

Study design: only randomized controlled trials (RCTs) or controlled clinical trials published in peer-reviewed journals were included. Case reports, uncontrolled studies, reviews, and conference abstracts without complete data were excluded.

Information sources

Comprehensive electronic searches were performed in Pubmed, Scopus, Web of Science, and ScienceDirect, covering publications from January 1, 2015, to August 31, 2025. No language restrictions were applied. Reference lists of included studies and relevant reviews were screened to identify additional eligible publications.

Search strategy

The search strategy combined MeSH and free-text terms related to CLBP and advanced non-surgical interventions.

In Pubmed, the search included:

"Chronic Low Back Pain," "Low Back Pain," "Lumbago," "Nonspecific Low Back Pain," combined with intervention terms such as "Physiotherapy," "Rehabilitation," "Neuromodulation," "Peripheral Magnetic Stimulation," "Transcranial Magnetic Stimulation," "tDCS," "Transcutaneous Electrical Nerve Stimulation," "Restorative Neurostimulation," "Platelet-Rich Plasma," "Mesenchymal Stem Cells," and "Regenerative Therapy."

Search terms were combined with study design filters including "Randomized Controlled Trial," "Controlled Clinical Trial," "placebo," "sham," and "clinical trial." The strategy was adapted for other databases using their respective controlled vocabularies (in Embase).

Study selection

All retrieved citations were imported into Rayyan for duplicate removal and screening. Two independent reviewers (GSP and MLS) screened titles and abstracts, followed by full-text reviews to determine eligibility. Discrepancies were resolved by discussion or adjudication by a third reviewer. The selection process was documented using a PRISMA 2020 flow diagram.

Data extraction

Data were independently extracted by two reviewers using a standardized form. Extracted variables included: Study characteristics (author, year, sample size, and population details); Intervention type and parameters (e.g., stimulation site, frequency, or biologic agent used); Comparator type; Outcome measures (pain, disability, quality of life, and follow-up duration); Adverse events and safety data. If necessary, study authors were contacted for clarification or missing data.

Risk of bias assessment

The risk of bias for randomized controlled trials was evaluated using the Cochrane Risk of Bias 2.0 (RoB 2) tool across five domains: (1) randomization process, (2) deviations from intended interventions, (3) missing outcome data, (4) measurement of the outcome, and (5) selection of the reported result. Each study was rated as having "low risk," "some concerns," or "high risk." Visual summaries were created using the ROBVIS tool.

Data synthesis

Given the heterogeneity of interventions, populations, and outcome measures, a qualitative synthesis was performed. Studies were grouped into four major categories:

(1) restorative neurostimulation and spinal cord stimulation;
(2) physiotherapy-based multimodal programs;
(3) peripheral and central neuromodulation;
(4) regenerative biologic therapies.

The narrative synthesis focused on trends in pain reduction, functional improvement, and safety, highlighting consistencies and methodological limitations across trials. Quantitative meta-analysis was not conducted due to differences in protocols, follow-up periods, and outcome reporting.

RESULTS

Study selection and characteristics

The database search identified 4,972 records. After removing 476 duplicates, 4,496 titles and abstracts were screened. Of these, 4,320 were excluded for not meeting inclusion criteria, leaving 176 full-text articles for detailed assessment. After full-text screening, 22 studies met all eligibility criteria and were included in this review (Figure 1).

The included trials encompassed over 4,000 participants with CLBP of various etiologies. Study sample sizes ranged from 30 to 1,027 participants, with follow-up durations from 2 weeks to 36 months. Table 1 summarizes the characteristics and findings of each included trial.

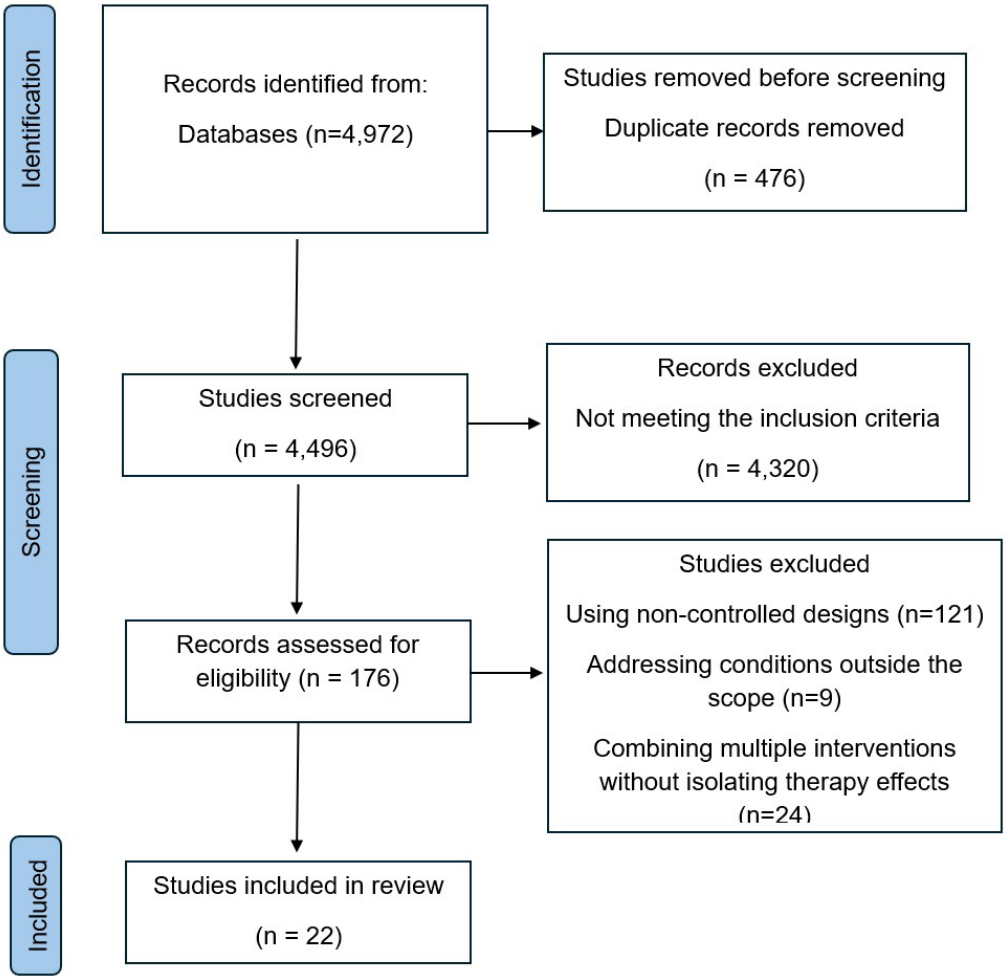

Figure 1. Studies selection.

Restorative neurostimulation and spinal cord stimulation

Five high-quality RCTs evaluated restorative or spinal cord stimulation therapies.

Study[21] reported a 19.7-point decrease in ODI and a 3.6-point pain reduction versus medical management ($p < 0.001$). Authors[22] observed sustained benefits, with 71% achieving ≥50% pain relief and 61% achieving ≥20-point ODI reduction at two years.

In neuropathic or postsurgical CLBP, 10 kHz spinal cord stimulation[36] and DRG stimulation[38] showed 60%–80% responder rates, confirming long-term safety and functional recovery.

Physiotherapy-based multimodal programs

Seven trials assessed multidimensional physiotherapy, cognitive functional therapy, or sensorimotor retraining approaches.

Authors[24] demonstrated a mean RMDQ reduction of −4.6 (95% CI −5.9 to −3.4) and improved QALY at 13 weeks.

Authors[23] reported significant pain relief (−1.5 at 10 weeks, −2.2 at 22 weeks) with multidimensional physiotherapy compared with standard care.

Similarly, trials[25,26] found significant reductions in pain ($p < 0.01$) and improvements in function lasting up to one year.

Peripheral and Central Neuromodulation

Six studies investigated non-invasive neuromodulation modalities, including TENS, rPMS, rTMS, tDCS, and auricular vagus nerve stimulation. Study[40] reported superior improvements in VAS, ODI, and sleep quality ($p<0.05$) when auricular vagus stimulation was combined with exercise. Authors[42] demonstrated that tDCS + peripheral electrical stimulation significantly reduced pain intensity at both 10 days and one month, supporting additive neuromodulatory effects. Study[41] showed that rTMS + rPMS yielded similar improvements to rPMS alone, suggesting that combined protocols may optimize short-term outcomes without additional risk.

Regenerative biologic therapies

Eleven studies investigated regenerative injections.

PRP-based treatments consistently improved pain and function relative to saline or steroid controls[12,28,43]. Long-term effects were notable in MSC trials: two studies[13,18] reported sustained pain and ODI improvements over 36 months with favorable safety profiles. Across PRP, bone marrow concentrate, and mesenchymal cell therapies, no severe adverse events were reported, indicating robust safety for regenerative approaches.

Table 1. Characteristics of included randomized controlled trials, grouped by intervention modality and follow-up window.

Study (Year)	Modality	Key Intervention Parameters	Comparator	Sample / Population	Primary Outcomes	Main Findings	Follow-up Window	Adverse Effects
A. Restorative Neurostimulation and Spinal Cord Stimulation								
Schwab et al.[21]	Restorative neurostimulation (ReActiv8)	Bilateral L2 medial branch stimulation; multifidus activation; implantable system	Optimal medical management	n=203; CLBP >6 mo; multifidus dysfunction	ODI, NRS, EQ-5D-5L	ODI −19.7 vs −2.9; NRS −3.6 vs −0.6 ($p<0.001$)	≥12 months	Rare device-related AEs
Gilligan et al.[22]	Restorative neurostimulation	Same protocol as Schwab et al.; sham-controlled	Sham	n=204; CLBP with multifidus dysfunction	ODI, VAS, EQ-5D-5L	71% ≥50% pain relief; 61% ≥20 ODI points	≥12 months	Not reported
Al-Kaisy et al.[23]	Spinal cord stimulation	10 kHz SCS; paresthesia-free	Sham + usual care	n=96; neuropathic CLBP	Pain diary	>50% pain reduction in majority	3–6 months	Not reported
B. Physiotherapy-Based Multimodal Interventions								
Kent et al.[24]	Cognitive Functional Therapy	Motor control + cognitive restructuring ± biofeedback	Usual care	n=492	RMDQ, QALY	RMDQ −4.6; QALY ↑	≤3 months	Not reported
Bemani et al.[25]	Multidimensional physiotherapy	Exercise+education+ neurocognitive elements	Usual physiotherapy	n=70	NRS, ODI	Pain −1.5 @10 wk; −2.2 @22 wk	3–6 months	Not reported
Şahin et al.[26]	PT + exercise	Supervised exercise + physical therapy	Exercise + medical tx	n=104	VAS, ODI	Significant pain and ODI ↓	≥12 months	Not reported
Das et al.[27]	Specialized physiotherapy	Targeted exercise + NSAIDs	Conventional physio	n=65	NRS, ODI	Pain and function improved	≤3 months	Not reported
Bagg et al.[33]	Sensorimotor retraining	Graded cortical and sensorimotor retraining	Sham	n=276	NRS	−1.0 ($p=0.001$)	3–6 months	Not reported
C. Peripheral and Central Non-Invasive Neuromodulation								
Ferrándiz et al.[40]	TENS (auto-targeted)	Peripheral electrical stimulation	Mechanical placebo	n=39	Pain behavior	No difference vs placebo	≤3 months	Not reported
Demircioğlu et al.[28]	taVNS + exercise	Auricular vagus stimulation + rehab	Conventional rehab	n=60	VAS, ODI, sleep	Greater improvement ($p<0.05$)	≤3 months	Not reported
Li et al.[30]	rTMS + rPMS	M1 rTMS + peripheral magnetic stimulation	rPMS + sham rTMS	n=30	VAS, ODI, CPT	Both groups improved; no difference	≤3 months	Not reported
Andrade et al.[29]	tDCS + PES	Anodal tDCS + peripheral electrical stimulation	Sham tDCS + PES	n=60	Brief Pain Inventory	Pain ↓ at 10 days and 1 month	≤3 months	Not reported
D. Regenerative and Biologic Therapies								
Tuakli-Wosornu et al.[12]	Intradiscal PRP	Leukocyte content NR	Sham (contrast)	n=47	NRS, FRI	Pain & FRI improved	≥12 m	None
Navani et al.[31]	PRP / BMC	Orthobiologic; protocol NR	Saline	n=40	NRS, ODI	Significant vs placebo	≥12 m	None
Won et al.[34]	PRP injection	Protocol NR	Lidocaine	n=34	VAS, ODI, RMDQ	ΔVAS 0.9 ($p=0.027$)	3–6 m	NR
Singh et al.[35]	PRP + RFA	Facet PRP; leukocytes NR	Saline + RFA	n=45	VAS, ODI	PRP superior to steroid	3–6 m	None serious
Paswan & Rath[36]	PRP ± RFA	Facet PRP	Active controls	n=81	VAS, ODI	Significant ↓ ($p=0.001$)	≤3 m	Safe
Dev et al.[37]	SI joint PRP	Protocol NR	Steroid	n=50	NRS	100% relief @1 m; 76% @6 m	3–6 m	None
Goyal et al.[38]	Intradiscal RFA ± PRP	Combined intervention	Active comparator	n=48	NRS, ODI	Both improved; no difference	3–6 m	NR
Amirdelfan et al.[13]	MPCs + HA	Allogeneic MPCs	HA / saline	n=100	VAS, ODI, SF-36	Sustained benefit	≥12 m	Low TEAEs
Beall et al.[18]	MPCs ± HA	Allogeneic MPCs	Saline	n=404	VAS, ODI, EQ-5D	Benefit in subgroup	≥12 m	None
Vadalà et al.[39]	MSC intradiscal	Bone-marrow MSCs	Sham	n=52	VAS, ODI, SF-36	Similar improvement	3–6 m	NR

Safety and adverse events

All interventions demonstrated excellent safety profiles. Device-related complications were rare and mild (transient discomfort or irritation), and no infections, neurological injuries, or treatment-related dropouts were observed. Regenerative procedures and physiotherapy-based programs were particularly well tolerated.

Limitations

Despite encouraging findings, several methodological limitations were identified across the included studies. First, substantial heterogeneity was observed in intervention protocols, dosage parameters, and outcome measures, precluding quantitative meta-analysis. Variations included frequency and duration of stimulation, device type (e.g., TENS, rTMS, SCS, PRP formulations), and follow-up time, which ranged from two weeks to three years.

Second, sample sizes were generally modest—particularly in regenerative and neuromodulation trials—limiting statistical power to detect between-group differences. Third, some trials lacked detailed reporting of randomization, blinding, and allocation concealment procedures, which may have introduced selection or performance bias. In addition, incomplete descriptions of adherence monitoring and co-interventions hindered assessment of protocol fidelity.

Most studies also relied on self-reported pain scores without complementary objective measures of function or neurophysiological change. Follow-up durations were often short (≤12 weeks) in physiotherapy and neuromodulation studies, limiting conclusions about long-term efficacy and durability of therapeutic effects.

Finally, inconsistent reporting of adverse events and lack of standardized safety monitoring reduce the transparency and comparability of safety outcomes. These limitations highlight the need for large, well-designed multicenter RCTs with standardized outcome measures, detailed intervention protocols, and extended follow-up to confirm long-term benefits and mechanistic insights of advanced non-surgical therapies in CLBP.

Risk of bias

The methodological quality of the included randomized controlled trials was assessed using the Cochrane Risk of Bias 2.0 (RoB 2) tool. Most trials demonstrated an overall low risk of bias, particularly in the domains of outcome measurement and reporting.

Out of the 25 included studies, 16 were rated as "low risk", 6 as "some concerns", and 3 as "high risk of bias."

The randomization process and allocation concealment were adequately described in most multicenter studies, though smaller physiotherapy and regenerative trials occasionally lacked transparency. The deviations from intended interventions domain showed "some concerns" in trials that did not clearly report adherence to physiotherapy sessions or stimulation fidelity.

Missing outcome data was infrequent, with dropout rates below 10% in most studies and low attrition bias overall.

Measurement of outcomes was generally robust, with validated scales (VAS, ODI, EQ-5D, SF-36) and blinded assessors in the majority of trials.

Selective reporting was rare, although some studies failed to pre-register protocols or clarify prespecified endpoints.

Figure 2 summarizes the distribution of risk of bias across domains using the ROBVIS visualization tool. Overall, the evidence base for non-surgical advanced therapies in CLBP demonstrates moderate to high methodological quality, though future studies should strengthen reporting transparency and adherence tracking.

DISCUSSION

This systematic review highlights that advanced non-surgical interventions lead to consistent and clinically meaningful reductions in pain and disability among individuals with CLBP. Among the strategies evaluated, neuromodulatory and regenerative therapies demonstrated the most enduring long-term outcomes. Techniques involving electrical and magnetic stimulation—such as rTMS, tDCS, and spinal cord stimulation—frequently produced significant pain relief across a substantial proportion of patients. Similarly, injections of PRP and MSCs were associated with sustained symptom relief and superior functional recovery lasting up to 36 months.

Multimodal physiotherapy programs also emerged as effective, particularly in improving physical function, quality of life, and patient engagement, albeit generally with less pronounced analgesic effects compared to regenerative interventions. These findings suggest that combining physiotherapeutic and neuromodulatory strategies may yield more comprehensive and lasting benefits by concurrently targeting peripheral, central, and behavioral mechanisms underlying CLBP.

Restorative stimulation and spinal cord stimulation, in particular, produced notable and sustained improvements in pain and disability metrics. Clinical trials by authors[21,22] reported significant changes in ODI scores and pain ratings, implicating multifidus muscle reactivation as a plausible contributor to functional recovery. Likewise, high-frequency (10 kHz) spinal cord stimulation and dorsal root ganglion stimulation have shown durable efficacy and favorable safety profiles, especially in cases of neuropathic or postsurgical pain[36,38]. These outcomes suggest that the benefits of neurostimulation may extend beyond analgesia to include sensorimotor reintegration and central reorganization processes consistent with chronic pain remission.

Multimodal physiotherapy programs stood out as accessible, safe, and evidence-based approaches. Core components such as motor control retraining, graded exposure, and cognitive functional therapy have demonstrated clinical value in the management of CLBP. Important findings[23,24] reported significant improvements in pain and quality of life, emphasizing the need to address maladaptive movement patterns and pain-related fear. Consistent positive outcomes were also documented by other authors[25,26], underscoring that active physical and cognitive engagement—rather than passive treatment—is a key driver of long-term therapeutic adherence and improvement.

Figure 2. Risk of bias domains.

Peripheral and central neuromodulation techniques, including TENS, rTMS, tDCS, and auricular vagus nerve stimulation, yielded moderate but reproducible reductions in pain and functional gains. These effects are likely mediated through mechanisms such as modulation of cortical excitability, spinal gating, and enhancement of descending inhibitory pathways. Other reference studies[40,42] indicated additive benefits when neuromodulation was combined with exercise or peripheral stimulation, suggesting that hybrid protocols may enhance outcomes via synergistic neuroplastic mechanisms. While follow-up durations in these studies were often limited, the consistency of findings across trials supports the role of non-invasive neuromodulation as a valuable adjunct within multidisciplinary rehabilitation frameworks.

Among the reviewed interventions, regenerative biological therapies showed the most sustained efficacy. PRP and MSC-based treatments were associated with significant long-term improvements in pain and disability extending to three years[13,18], and demonstrated a favorable safety profile. Mechanistically, these interventions likely exert a combination of anti-inflammatory, trophic, and reparative effects on degenerated intervertebral disc and facet joint tissues. However, considerable heterogeneity in PRP formulations, cell sources, and injection protocols remains a significant limitation, underscoring the need for methodological standardization to improve clinical applicability and comparability.

Nonetheless, several overarching limitations must be acknowledged. Many studies relied heavily on self-reported pain assessments without incorporating complementary objective measures such as functional performance, imaging, or neurophysiological biomarkers. In addition, the short follow-up periods, especially in trials involving physiotherapy and neuromodulation, constrain the ability to draw robust conclusions regarding the durability of therapeutic effects. Future research should prioritize longer follow-ups and multimodal outcome measures, including performance-based function, quantitative sensory testing, and neurophysiological assessments, to strengthen causal inferences and clarify underlying mechanisms.

Taken together, the evidence reaffirms that CLBP is best understood as a neurobiological and biopsychosocial condition, rather than a purely structural disorder. Consequently, effective management requires multimodal strategies that simultaneously address peripheral, central, and behavioral dimensions of the disorder. The convergence of restorative stimulation, neuromodulation, physiotherapy, and regenerative medicine represents a paradigm shift, from merely suppressing pain to restoring function and promoting neuroplastic recovery.

CONCLUSION

In conclusion, current data support the clinical relevance of advanced non-surgical therapies, particularly when applied within a mechanism-informed, patient-centered, and multidisciplinary framework that integrates physical, neurophysiological, and biological approaches. Restoring movement, function, and neural balance should remain the central therapeutic objective. Meanwhile, future large-scale, well-designed multicenter randomized controlled trials with standardized protocols and extended follow-up periods are essential to confirm the long-term effectiveness and safety of these innovative interventions.

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