

ORAL OPIOID ANALGESICS VS SPINAL STEROID INJECTIONS IN THE TREATMENT OF LOW BACK PAIN: A COMPREHENSIVE SYSTEMATIC REVIEW

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ABSTRACT

Introduction: Low back pain (LBP) affects a significant portion of the population worldwide, with distinct treatment needs for acute and chronic cases. Despite widespread opioid use, evidence for their efficacy in LBP remains uncertain, highlighting the need for alternative interventions. Minimally invasive procedures like epidural steroid injections offer potential relief for conditions like lumbar disc herniation, but their effectiveness is debated. To address these complexities, we conducted a comprehensive review encompassing various treatment modalities beyond medication, aiming to optimize outcomes and improve quality of life for individuals with LBP.

Method: The researchers in this study followed the 2020 Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines to ensure that their work met the required standards. This was done to ensure the precision and reliability of the conclusions derived from the research.

Result: Our search produced 13 results. After looking at the titles and summaries, we found 8 papers that fit our criteria. At first, we excluded several articles because they were written in review style and case reports. But after reading the full papers carefully, we included four papers in our final analysis. These papers included retrospective analysis, a randomized, double blind, placebo controlled cross-over study, noninterventional, retrospective 12-week study using anonymized clinical practice data from the German Pain eRegistry, and a retrospective analysis of anonymized, propensity score-matched data.

Conclusion: Favorable post-injection outcomes suggest the blind method for caudal epidural injections is safe and effective, suitable for patients not eligible for surgery or unresponsive to conservative treatments. Interlaminar epidural steroid injections effectively reduce VAS and ODI scores in patients with chronic low back pain and multi-level disc disease, but further research is needed to standardize administration protocols and optimize treatment outcomes, including addressing BMI's impact. The analgesic efficacy of periradicular meloxicam injections for acute/subacute low back pain, indicating a potential new treatment option, while real-world data suggest NBX oromucosal spray may be superior to typical oral LAO analgesics for severe peripheral NBP, pending confirmation in large RCTs.

Keywords: Oral opioid, epidural steroid injection, low back pain, sciatica pain

INTRODUCTION

Low back pain (LBP) is a prevalent health issue, affecting over 70% of individuals in industrialized nations and with a global lifetime prevalence of 84%. Over the past two decades, numerous guidelines have been developed for its management, primarily emphasizing medication use.¹ However, it's crucial to recognize that acute and chronic LBP require distinct treatment approaches due to their differing nature and implications. Acute LBP, which can progress to chronic status, significantly impacts quality of life and functionality. Initial conservative treatments for acute LBP may not always be effective, and identifying patients at risk of prolonged symptoms is essential for appropriate triage and therapy selection.²

Despite the widespread use of opioid analgesics for LBP, uncertainties persist regarding their efficacy, optimal dosing, and patient tolerability, particularly in the context of long-term use. Recent systematic reviews highlight the lack of robust evidence supporting the efficacy of opioids for acute and chronic LBP.³ Additionally, questions arise regarding the tolerability and response of opioid-naïve individuals to these medications, given the exclusion criteria often applied in clinical trials.³

Furthermore, while lumbar disc herniation (LDH) is a leading cause of LBP, inflammatory processes also play a significant role in its etiology, necessitating interventions to reduce inflammation. Conservative treatments like bed rest, medical therapy, and physical therapy are commonly prescribed, yet a small percentage of cases progress to chronicity, prompting consideration of alternative interventions.⁴ Minimally invasive procedures such as epidural steroid injections (ESIs) have emerged as a viable option for diagnosing and managing LDH-related LBP. However, the effectiveness of these procedures remains a subject of debate, with conflicting evidence regarding their efficacy and optimal administration routes. Managing LBP requires a nuanced approach considering the distinct nature of acute and chronic presentations and the uncertainties surrounding medication efficacy and alternative interventions like ESIs.⁵

In previous guidelines, focusing mainly on medication, had limitations. Therefore, we conducted a comprehensive review, encompassing various treatment modalities such as general behavioral strategies, pharmacotherapy, psychological interventions, exercise, rehabilitation, education, physical modalities, and invasive procedures. These approaches were meticulously evaluated and graded to provide a more nuanced framework for managing both acute and chronic LBP. This comprehensive approach aims to optimize outcomes and improve the quality of life for individuals suffering from LBP.

METHODS

Protocol

The researchers in this study followed the 2020 Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines to ensure that their work met the required standards. This was done to ensure the precision and reliability of the conclusions derived from the research.

Criteria for Eligibility

For inclusion in the study, published articles had to meet particular requirements. They had to be research papers written in English, focusing on oral opioid analgesics and spinal steroid injections in the treatment of low back pain. The studies had to meet the following criteria: articles need to have been published after 2016 but within the applicable timeframe for this systematic review. Articles falling into categories like editorials, lacking a DOI, review articles that were already published, or duplicating previously published journal papers were excluded from the assessment.

Search Strategy

We conducted a comprehensive literature search using PubMed, Wiley Journal Database, and ScienceDirect focusing on studies published from 2016 to 2024. The search terms employed were as follows ("mouth"[MeSH Terms] OR "mouth"[All Fields] OR "oral"[All Fields]) AND ("analgesics opioid"[Pharmacological Action] OR "analgesics, opioid"[MeSH Terms] OR ("analgesics"[All Fields] AND "opioid"[All Fields]) OR "opioid analgesics"[All Fields] OR "opioid"[All Fields] OR "opioids"[All Fields] OR "opioid s"[All Fields]) AND ("low back pain"[MeSH Terms] OR ("low"[All Fields] AND "back"[All Fields] AND "pain"[All Fields]) OR "low back pain"[All Fields]) and ("mouth"[MeSH Terms] OR "mouth"[All Fields] OR "oral"[All Fields]) AND ("analgesics opioid"[Pharmacological Action] OR "analgesics, opioid"[MeSH Terms] OR ("analgesics"[All Fields] AND "opioid"[All Fields]) OR "opioid analgesics"[All Fields] OR "opioid"[All Fields] OR "opioids"[All Fields] OR "opioid s"[All Fields]) AND ("low back pain"[MeSH Terms] OR ("low"[All Fields] AND "back"[All Fields] AND "pain"[All Fields]) OR "low back pain"[All Fields]). Moreover, we performed cross-referencing of relevant articles to reveal additional research. The evaluation of study quality, methodology, interventions, and results was undertaken independently by the researchers, resolving any differences through discussion and agreement. Furthermore, both researchers collected and compared discoveries from all studies, considering the potential for conducting a meta-analysis if deemed feasible.

Inclusion and exclusion criteria

Inclusion criteria for the studies were as follows: (1) original research that assesses oral opioid analgesics and spinal steroid injections in the treatment of low back pain; (2) Randomized Controlled Trials (RCTs) or observational studies (cohort or case-control studies); (3) availability of relevant data. Exclusion criteria were as follows: (1) ongoing studies or studies without available data; (2) duplicate publications. In cases of duplicate publications, the most recent article was chosen; (3) Non-English language studies were excluded.

Data Retrieval

The authors conducted a thorough examination of relevant studies, specifically selecting those that met precise inclusion criteria. They focused on original, unpublished papers in English to ensure a refined and high-quality selection. The analysis covered essential information, such as study particulars, authors, publication dates, locations, and research methodologies, aligning with the study's objectives

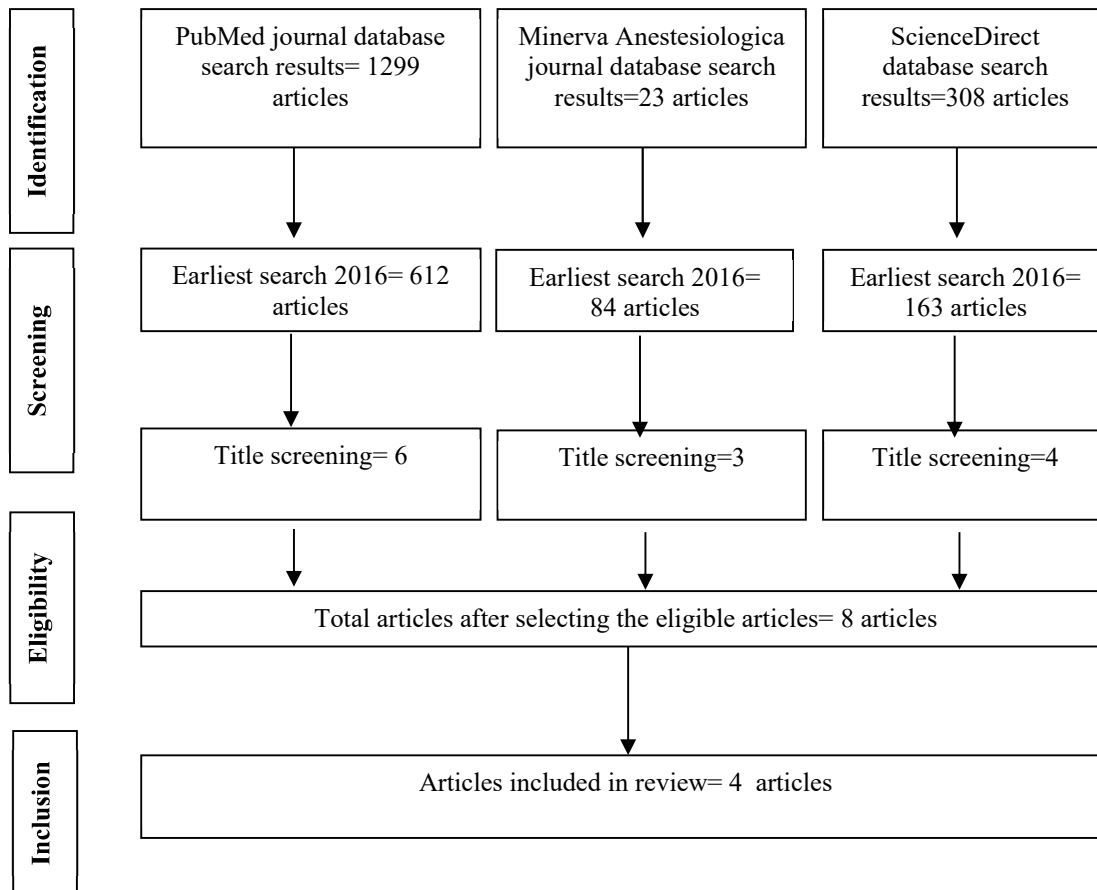


Figure 1. Article search flowchart

Author	Origin	Method	Sample	Result
Dernek et al., 2022. ⁶	Turkey	Retrospective analysis.	107 patients who had been given CEI between September 2017 and January 2018.	The most common disc pathology was at the L4–L5 level. The VAS and ODI scores indicated significantly reduced pain at 3 and 6 months compared with the pre-injection baseline. Two patients experienced total anesthesia and paresis of the lower limbs, but recovered fully after 2 weeks. Blood was aspirated during the injection in two patients, but second-attempt injections were successful in both cases. No other complications were observed.
Ökmen, et al., 2016. ⁷	Italy	a randomized, double blind, placebo controlled cross-over study.	80 consenting patients suffering LBP.	The baseline NRS was 9.3 (95% CI: 8.9-9.7) in the C-group and 9.2 (95% CI: 8.8-9.6) in the M-group. At the 24 hours follow-up after the initial treatment, the mean NRS was 6.3 (95% CI: 5.4-7.2) in the C-group vs. 3.5 (95% CI: 2.6-4.4) in the M-group (P<0.05). The number of cross-over cases was significantly higher in the C-group (N.=31, 77.5% vs. N.=5, 12.5%, P<0.001). At the 3 months follow-up, 66 patients (35+31) were allocated in the M-group and 54 (82%) reported NRS Score <3, while only 14 (9+5) patients remained in the C-group and eight patients had NRS<3.
Aurini et al., 2016. ⁸	Germany	Noninterventional , retrospective 12-week study using anonymized clinical practice data from the German Pain eRegistry.	Propensity score matching resulted in datasets of 2331 patients for each treatment group.	All six single criteria showed significantly better outcomes for tapentadol PR (all parameters p < 0.001). There were significantly more treatment responders under tapentadol PR (65.7 vs 14.2%; p < 0.001).
Ueberall et al, 2022.	Australia	Retrospective analysis of anonymized, propensity score-matched data from the German Pain e-Registry of adult outpatients who initiated NBX or LAO between March 2017 and March 2020.	Data were analyzed from propensity score-matched patients treated with NBX (n=655) or LAO (n=655)	Data were analyzed from propensity score-matched patients treated with NBX (n=655) or LAO (n=655); mean age 51 years; 57% female; mean pain duration 2.6 years; chronic pain 61%; severe dysfunctional pain 93%. At 6 months, NBX was noninferior to LAO for overall symptom relief, based on the least-squares mean difference between cohorts in change from baseline in patient-reported, pain-related aggregated nine-item scale scores (27.84%; 95% confidence interval [CI] 29.71 to 25.96; P<0.001) and individual pain-related scale scores. Subsequent prespecified superiority analysis of the primary endpoint showed that NBX was superior to LAO: all secondary endpoints measuring symptoms of pain and physical function improved significantly with NBX and LAO, with between-group differences favoring NBX (all P<0.001). Fewer patients treated with NBX than LAO experienced treatment-related adverse events (25.5% vs 76.0%; P<0.001) or discontinued treatment because of treatment-related adverse events (7.9% vs 29.3%; P<0.001).

RESULT

Our search produced 13 results. After looking at the titles and summaries, we found 8 papers that fit our criteria. At first, we excluded several articles because they were written in review style and case reports. But after reading the full papers carefully, we included four papers in our final analysis. These papers included retrospective analysis, a randomized, double blind, placebo controlled cross-over study, noninterventional, retrospective 12-week study using anonymized clinical practice data from the German Pain eRegistry, and a retrospective analysis of anonymized, propensity score-matched data.

Dernek et al. in 2022 examined the effectiveness of blind caudal epidural injections, without radiological guidance, in alleviating pain and improving functional status in patients with lumbar disc disease. This retrospective study assessed

complications and tracked outcomes in 162 patients who underwent the procedure. Among them, 27 patients were lost to follow-up, and 12 required surgery post-injection. Follow-up evaluations were conducted for the remaining 123 patients, of whom 107 were included in the analysis. The majority were female laborers, with the most common disc pathology found at the L4–L5 level.⁶

Analysis of Visual Analog Scale (VAS) and Oswestry Disability Index (ODI) scores revealed significantly reduced pain levels at 3 and 6 months post-injection compared to baseline. Although two patients experienced temporary lower limb anesthesia and weakness, both fully recovered within two weeks. Blood aspiration occurred in two cases during injection, but successful second attempts were made without further complications.⁶

This study aimed to assess the effectiveness of ILES administration in patients with multi-level lumbar disc pathology (LDP). Our analysis found no statistically significant differences between the groups in terms of demographic variables, duration of disease, or procedural details ($p > 0.05$). Additionally, there were no significant differences in pain and functional scores (PRT VAS and ODI) between the groups ($p > 0.05$). However, significant differences were observed within both groups across different measurement points ($p < 0.05$), with multiple comparison tests revealing distinct intervals of variance.⁷

Between-group comparisons demonstrated significant differences in VAS and ODI scores at one, three, six, and 12 months ($p < 0.05$), with consistently higher scores in Group L compared to Group S. Subsequent analyses showed no significant differences in VAS and ODI scores between Group S and Group L patients requiring a second injection ($p > 0.05$). However, significant intra- and intergroup differences were observed in pain and functional scores at subsequent measurement points post-second injection ($p < 0.05$), with Group S patients exhibiting lower scores.⁷

Correlation analyses revealed no significant associations between age and pain/functionality scores, or between BMI and disease duration or pain/functionality scores ($p > 0.05$). However, a negative correlation was observed between age and disease duration ($r = -0.22$), indicating statistical significance ($p < 0.05$).⁷

A randomized, double-blind, placebo-controlled, cross-over study to investigate the efficacy of periradicular injections of meloxicam in reducing pain scores by 50% or more compared to a saline control group among patients experiencing recent onset of LBP (<6 months). Our secondary objective was to demonstrate a 50% reduction in the need for analgesic medications and an improvement in physical activity level and quality of sleep. The demographic characteristics of the two study groups are outlined in Table I, revealing no significant differences in the background history of LBP between the treatment groups.⁸

The study results indicated a statistically significant difference in Numeric Rating Scale (NRS) scores for pain within the first 24 hours, with notable divergence between the two groups beginning at six hours post-injection. Overall changes in NRS scores are depicted in Figure 5. Following the initial injection, a substantial proportion of patients initially treated with meloxicam remained in this group, while a significantly higher number of patients in the control group opted for cross-over ($p < 0.001$).⁸

By the end of the 90-day evaluation period, a greater number of patients were allocated to the meloxicam group, with the majority experiencing substantial pain relief. Of note, some patients withdrew from the study due to reasons such as lack of perceived benefits or refusal of additional injections. Among those initially allocated to meloxicam, a majority experienced pain reduction exceeding 50%, with varying numbers of injections required for sustained relief. The success rate, defined as NRS Score <3 at the 90-day follow-up, was significantly higher in the meloxicam group compared to the control group ($\chi^2 = 4.0$, $p = 0.045$).⁸

Notably, there was an improvement in LBP-related symptoms observed during the 90-day follow-up. However, some patients still required analgesic "rescue" medication, with a portion necessitating opioid analgesics. Among patients with herniated disk disease (HDD), meloxicam treatment resulted in satisfactory pain relief for the majority. Additionally, patients with a history of prior low back surgery ('failed back syndrome') experienced varying degrees of pain relief, with some opting for cross-over to meloxicam injections for enhanced efficacy.⁸

The main aim of study was to compare the effectiveness of NBX oromucosal spray against LAO analgesics in patients with neuropathic back pain, utilizing a composite primary endpoint consisting of various self-reported pain measures. Secondary objectives included assessing the safety and tolerability of NBX versus LAO by examining treatment-related adverse events (TRAEs) and treatment discontinuations due to TRAEs.⁹

Regarding the study population, after applying selection criteria, 655 patients receiving NBX oromucosal spray and an equal number of propensity-matched patients receiving oral LAO analgesics were analyzed. Over the 6-month evaluation period, a significantly lower proportion of patients treated with NBX (29.3%) discontinued treatment compared to those treated with LAO (46.0%), mainly due to drug-related adverse events. Demographic and baseline characteristics between the NBX and LAO cohorts showed no clinically relevant differences.⁹

Patients in both groups exhibited significant reductions in pain and improved functionality over time. However, patients treated with NBX consistently demonstrated better outcomes compared to those treated with LAO, with significantly higher reductions in pain intensity and disability scores at various time points. Additionally, a larger proportion of NBX-treated patients achieved clinically meaningful improvements in pain relief compared to LAO-treated patients. Furthermore, NBX was associated with a significantly lower incidence of treatment-related adverse events compared to LAO, resulting in fewer treatment discontinuations due to adverse events. Subgroup analyses further supported the superiority of NBX over LAO in improving pain intensity and achieving clinically meaningful pain relief.⁹

DISCUSSION

Epidural injections are frequently administered blindly due to the unavailability of radiological screening equipment and to minimize treatment expenses. The commonly used blind technique involves palpating the sacral horn, followed by local anesthesia administration and confirming sacrococcygeal ligament penetration by the spinal needle.⁹ However, the reported misinjection rate with this method is 25–30%, particularly higher in cases of anatomical variation. In the study, researchers drew an equilateral triangle between the sacral hiatus apex and the bilateral posterior superior iliac spines while the patient was in the prone position. This method was similar to Senoglu et al.'s approach, although they didn't report clinical outcomes, hindering direct comparison with our findings.¹⁰

Common complications of blind injections include needle misplacement, subarachnoid puncture, and intrathecal or intravascular injection. The rate of incorrect injection site localization with repeated attempts ranges from 11% to 42%. In our study, needle misplacement occurred in two cases, but the injection wasn't administered due to detected aspirated blood, indicating incorrect localization. Successful placement was achieved in both cases with a second attempt.⁹ Studies comparing different techniques, such as guided caudal injection under ultrasonographic guidance, have shown varying rates of complications. For instance, intravascular injection rates ranged from 0% to 24% depending on the method used. In our study, two patients experienced lower-extremity numbness post-injection, but they fully recovered within two weeks.¹¹ Despite potential limitations such as the lack of radiological visualization and a control group, the study suggests that favorable clinical outcomes and low complication rates can be achieved with blind caudal epidural injections guided by anatomical landmarks in patients with chronic low back pain.⁹

In the current investigation, research employed interlaminar epidural steroid administration in patients diagnosed with chronic low back pain and multi-level disc disease. Those who received a combination of a local anesthetic and steroid exhibited significantly lower Visual Analog Scale (VAS) and Oswestry Disability Index (ODI) scores at the one-year follow-up visit. The findings underscored the efficacy of this combination, particularly favoring a mixture with high-volume saline procaine for initial pain relief in chronic low back pain cases. However, subsequent studies in the literature have highlighted the significant role of corticosteroid (CS) injections.⁷

There exists a debate regarding the efficacy of epidural steroid injections, with various studies reporting different outcomes. Some studies have demonstrated efficacy, while others have shown only moderate effectiveness or inefficacy. The choice of drugs and their doses, including CSs like betamethasone, methylprednisolone, and triamcinolone, used alone or in combination with local anesthetics, varies among studies. For instance, the efficacy of interlaminar epidural steroid injections has been demonstrated in studies using mixtures of 10 mL local anesthetic plus steroids. However, reduced efficacy has been observed in follow-up visits after six months.¹² Conversely, studies reporting inefficacy of such injections often employed methylprednisolone 80 mg, with differing combinations of local anesthetics and saline. The study contributes to this discussion by showing the benefits of using a mixture of methylprednisolone 40 mg/10 mL and bupivacaine 0.25% in reducing VAS and ODI scores, aligning with findings from existing literature.¹³ Notably, despite the focus on multi-level disc pathology in some studies, the investigation favored an interlaminar approach over a caudal approach due to the former's ability to accommodate higher drug volumes and its non-inferiority compared to the latter approach in literature.⁷

Moreover, the study took into account factors influencing the success of interlaminar epidural steroid injections. We found that patient positioning for 30 minutes post-injection facilitated drug distribution, while using a lower steroid dose (40 mg instead of 80 mg) potentially affected fluid viscosity and increased anterior flow. Additionally, the inclusion of saline in our protocol might have helped in removing adhesions in the epidural space, as suggested by previous studies.⁷

Acute and subacute low back pain (LBP) is commonly treated with paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) as the first-line option, despite their limited efficacy and well-known side effects. In our initial case-series, our research group explored the periradicular administration of the generic NSAID meloxicam, which showed promising preliminary findings.¹⁴ This approach was chosen because meloxicam was available for parenteral administration and initial results suggested a positive impact on functional recovery. Second-line medications often include opioids, but their use is associated with side effects and unreliable recovery of functional activity. Muscle relaxants and benzodiazepines lack scientific evidence, and the combination of morphine and benzodiazepine has not shown significant advantages over morphine alone, while prolonging emergency department stays. Recent attempts to administer intravenous lidocaine were ineffective.¹⁵

Non-pharmacologic strategies such as acupuncture and electrical nerve stimulation have reported short-term improvements, but evidence supporting their efficacy, even in acute LBP, is lacking. However, there is moderate evidence supporting manipulation and soft tissue techniques combined with standard medical care.¹⁶ Bed rest has been found to be ineffective, and general practitioners have shown better outcomes in treating acute LBP compared to referrals to orthopedic surgeons. Building upon the promising results of our preliminary case-series with meloxicam, researchers designed a prospective, randomized, double-blind, placebo-controlled crossover study to investigate periradicular injection of meloxicam versus saline (control). Meloxicam, a selective COX-2 inhibitor, has demonstrated anti-inflammatory efficacy and safety in various conditions, including LBP.⁸

The mechanism responsible for meloxicam's sustained analgesic efficacy when infiltrated periradicularly remains unclear. Animal studies have shown an inverse relationship between plasma meloxicam concentrations and certain blood parameters, suggesting a systemic anti-inflammatory effect. Clinical studies have demonstrated sustained pain relief with meloxicam in various conditions, including discogenic compressive radicular syndrome and lumbosacral intervertebral osteochondrosis complicated by secondary radiculopathy. The periradicular route of administration, similar to an intramuscular injection but closer to the target site of inflammation, provides a rational therapeutic option for localized nerve root inflammation. While our controlled clinical trial showed encouraging findings, further dose-ranging studies are necessary to determine the optimal therapeutic dose of meloxicam for acute/subacute LBP.

Additionally, saline injections in the study also showed some beneficial effects, possibly due to local actions such as dilution of pro-inflammatory substances and changes in pH. Other authors have reported similar results, suggesting various mechanisms such as the placebo effect and suppression of ectopic discharges from inflamed nerves. For patients with recent-onset LBP, spontaneous resorption of acutely herniated discs is a major cause of symptom reduction within the first six months.¹⁶ Non-surgical treatments such as periradicular meloxicam injections offer a less invasive option, especially when administered early after symptom onset. Moreover, evidence supports the cost-effectiveness of interdisciplinary interventions and early targeted treatment of LBP symptoms.¹⁷

This study aimed to compare the effectiveness and tolerability of NBX oromucosal spray with traditional oral LAO analgesics in a real-world setting, focusing on patients with severe NBP who hadn't achieved sufficient pain relief with standard systemic therapy.⁹ Through propensity score matching, demographic and clinical factors were controlled, resulting in a matched population, predominantly with chronic and severe dysfunctional pain. The majority had tried multiple previous pain medications and were taking several background pain medications at baseline. Comorbidities were common, with about four per patient on average.

An initial analysis showed that NBX oromucosal spray was non-inferior to LAO analgesics in relieving severe NBP, followed by a subsequent analysis demonstrating its superiority. Secondary endpoints, including individual components of pain and physical function, significantly improved in both groups, with NBX consistently outperforming LAO. Subgroup analysis reinforced these findings, especially in patients with high baseline pain intensity.⁹ These results build upon a previous exploratory analysis involving NBX oromucosal spray for chronic pain, showing its superiority in providing symptom relief, particularly in patients with neuropathic pain. Additionally, a systematic review of RCTs highlighted the effectiveness of NBX as add-on therapy for chronic neuropathic pain.¹⁸

Regarding tolerability, NBX exhibited a superior profile compared to LAO, with fewer patients reporting treatment-related adverse events or discontinuing treatment due to them. Incidences of adverse events were significantly lower in the NBX cohort. While this study has limitations inherent to observational designs, such as the inability to account for hidden characteristics and non-pharmacological treatments, propensity score matching helped to mitigate confounding factors. The use of ASR-9 scores, though not scientifically validated, offers a comprehensive approach to pain management, aligning with routine clinical practice.⁹

CONCLUSION

In as study, favorable post-injection clinical outcomes were observed, indicating the safety and efficacy of the blind method for administering caudal epidural injections to patients with chronic low back pain. This approach may be recommended for patients who are not candidates for surgery or have not benefitted from conservative treatments. Furthermore, the investigation revealed that interlaminar epidural steroid injections effectively reduce VAS and ODI scores at one-year follow-up in patients with chronic low back pain and multi-level disc disease. However, the lack of standardized protocols for epidural steroid administration necessitates further research to optimize injection techniques, steroid doses, and considerations like BMI's effect on treatment success.

Additionally, a prospective, randomized, double-blind, placebo-controlled cross-over study demonstrated the analgesic efficacy of periradicular injection of meloxicam in patients with acute/subacute low back pain. This suggests that periradicular administration of meloxicam could be a promising new treatment option for patients experiencing acute/subacute LBP. In conclusion, based on the analysis of anonymized real-world data, add-on treatment with NBX oromucosal spray was found to be superior to and better tolerated than typical oral LAO analgesics in patients with severe peripheral NBP inadequately controlled by recommended systemic therapy. However, further large, well-designed

prospective RCTs are needed to confirm the effectiveness and tolerability of NBX oromucosal spray in this patient population. In the interim, clinicians can consider these findings when making treatment decisions for similar patients in clinical practice.

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