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Beyond Oral Opioids? A Retrospective Comparison of Transdermal Buprenorphine and Oxycodone/Naloxone for Sustained Relief in Chronic Low-Back Pain

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Abstract

Introduction: Chronic low-back pain (CLBP) is a leading cause of disability, often requiring opioid therapy when conservative treatments fail. Transdermal buprenorphine and oral oxycodone/naloxone are commonly used, but their comparative effectiveness and safety remain underexplored. **Materials and Methods:** In this retrospective cohort study, 173 patients with CLBP treated at our center between June 2022 and May 2024 were analyzed. Group A (n = 88) received transdermal buprenorphine (5–15 µg/h), while Group B (n = 85) was treated with oral oxycodone/naloxone (10/5–20/10 mg/day). Treatment lasted four weeks, with dose titration after one week if pain was uncontrolled. Pain intensity (VAS), functional status (ODI), rescue medication use, and adverse effects were assessed at baseline and during follow-up. **Results:** Both groups showed significant reductions in VAS and ODI scores. Buprenorphine led to a greater functional improvement (ODI reduction $p = 0.04$) and a trend toward greater pain reduction (VAS $p = 0.08$). Rescue drug use was significantly lower in Group A (53.4%) compared to Group B (78.8%, $p = 0.003$). Adverse events were more frequent in the oxycodone group, particularly nausea and constipation. **Conclusions:** Transdermal buprenorphine provided comparable or superior analgesia with better tolerability and reduced reliance on rescue medication. It represents a safer, effective alternative for CLBP management in routine clinical practice.

Keywords: chronic low back pain; transdermal buprenorphine; oxycodone/naloxone; opioid therapy; pain management; Visual Analog Scale (VAS); Oswestry Disability Index (ODI); rescue medication; analgesic efficacy; adverse effects; retrospective cohort study

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1. Introduction

Chronic low-back pain (CLBP) is one of the most pervasive and disabling musculoskeletal disorders worldwide, exerting immense effects on individual functioning, societal

productivity, and health-care resource utilization [1,2]. Defined as pain localized below the costal margin and above the lower gluteal folds persisting for more than 12 weeks, CLBP frequently produces substantial impairment in activities of daily living, reduces health-related quality of life, and is associated with comorbid mood disturbances and sleep disruption [1,2]. Globally, low-back pain ranks among the leading causes of years lived with disability and imposes a disproportionate economic burden via direct costs (medical visits, imaging, medications, interventional procedures) and indirect costs (lost work days, reduced productivity) [2].

Management of CLBP is necessarily multimodal and frequently individualized, integrating pharmacologic, physical, and behavioral interventions, and occasionally interventional or surgical approaches when indicated [3]. Conservative measures—exercise therapy, manual therapy, cognitive-behavioral approaches, and nonsteroidal anti-inflammatory drugs (NSAIDs)—are the mainstay for the majority of patients. However, a substantial subset of patients remain symptomatic despite these therapies and may require escalated analgesic strategies [3–5]. In that circumstance, opioids are commonly considered for short- to intermediate-term relief of moderate-to-severe CLBP in carefully selected patients, though their use remains controversial due to concerns about tolerance, dependence, misuse, adverse events, and uncertain long-term effectiveness [6].

Within the opioid armamentarium, pharmacologic heterogeneity translates into distinct efficacy and safety profiles. Buprenorphine—a semi-synthetic opioid with partial agonist activity at the μ-opioid receptor and antagonism at the κ-opioid receptor—occupies a unique pharmacodynamic niche [6,7]. Its partial agonist activity confers strong analgesia while theoretically attenuating maximal μ-receptor-mediated respiratory depression and other dose-limiting adverse effects relative to full agonists. Furthermore, κ-antagonism may have salutary effects on mood and could mitigate opioid-induced hyperalgesia in some contexts [6,8]. When administered transdermally, buprenorphine delivers a continuous, low-fluctuation plasma concentration that minimizes peak-trough variability and may reduce peak-related adverse events; the patch format also offers practical advantages for patient adherence in populations with polypharmacy or swallowing difficulties [6,9].

Oxycodone is a prototypical full μ-opioid receptor agonist widely used in oral formulations for moderate-to-severe pain. It is effective at reducing nociceptive pain but is associated with common opioid-related adverse events—gastrointestinal effects (nausea, constipation), somnolence, dizziness—and carries a higher theoretical risk for rapid tolerance and dose escalation compared with partial agonists [10]. Combining oxycodone with naloxone in oral formulations aims to retain analgesia while limiting opioid-induced constipation through localized antagonism in the gut lumen; nonetheless, systemic opioid-mediated adverse events persist. Direct, contemporary comparisons of transdermal buprenorphine and oral oxycodone/naloxone in CLBP under pragmatic clinical conditions are limited.

Given the ongoing need to balance analgesic effectiveness with safety, tolerability, and opioid stewardship, head-to-head comparisons of different opioid modalities in CLBP are clinically valuable. The transdermal route of administration for buprenorphine introduces particular considerations: slower onset of steady-state concentrations may necessitate temporary rescue analgesics; however, once established, transdermal delivery may provide more uniform pain control and reduced incidence of peak-dose adverse events. Oxycodone/naloxone, with its rapid oral absorption, can produce faster early analgesia but at the potential cost of more frequent adverse effects and requirement for dose escalation. Direct real-world evidence comparing these two approaches in CLBP can inform prescribing decisions, particularly for patients who have exhausted non-opioid strategies.

The present retrospective cohort study therefore aimed to compare the short-term analgesic efficacy and tolerability of transdermal buprenorphine versus oral oxy-

codone/naloxone in patients with CLBP who had not achieved satisfactory relief with NSAIDs and physiotherapy. The primary outcome was the change in pain intensity measured by the Visual Analogue Scale (VAS) at four weeks; secondary outcomes included functional change by Oswestry Disability Index (ODI), frequency of dose titration, rescue analgesic use, and adverse events. We hypothesized that both regimens would produce clinically meaningful pain reduction but that transdermal buprenorphine would demonstrate superior tolerability and lower requirements for dose escalation and rescue medication.

2. Materials and Methods

2.1. Study Design and Population

This work represents a retrospective cohort study conducted at our institution on patients referred to our emergency unit or to our spinal surgery outpatient for CLBP between June 2022 and May 2024. This study was performed according to the STROBE guidelines [11]. The patients had previously received pharmacological therapy with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) with repeated courses of physiotherapy (manual, instrumental or physical exercises protocols), without satisfactory pain relief. In addition, before participating in this research, all patients had radiographic (X-ray) and magnetic resonance imaging (MRI) examinations of lumbosacral spine performed. This was carried out to rule out fractures, infectious diseases, or oncologic conditions as the etiologic reason underlying low-back pain.

It is routine practice to include all patients presenting to our emergency department with low-back pain (LBP) in a database. Routine data collection includes: age, gender, smoking history, pain on the VAS, and functionality on the ODI questionnaire. Routine clinical re-assessments are performed at every follow-up outpatient consultation. The same practice is routinely carried out in first-seen patients with LBP attending the specialized spinal surgery outpatient clinic. Although the study included standardized treatment protocols and scheduled assessments at weeks 1, 2, and 4, these were part of the institution's established clinical practice for CLBP management. The present analysis is therefore retrospective, based on review of routinely collected data, rather than a prospectively planned trial.

2.2. Inclusion and Exclusion Criteria

The inclusion criteria were: adults aged 18–75 years, with documented diagnosis of CLBP with duration of at least 12 weeks, baseline VAS for pain > 5 and a satisfactory data set. The exclusion criteria were: past history of spinal surgery in the previous year, conclamate and painful spinal pathologies (e.g., fractures, tumor, infection), psychiatric illness, active drug abuse, pregnant or lactating woman, neuromuscular disease, allergy or contraindication to drugs or rescue medication in this study, moderate or severe renal impairment, severe hepatic or cardiac impairment, past history of gastrointestinal disorders, bleeding disorders, asthma, epilepsy, any contraindication to use of opioids and having neuropathic pain or neurological deficit was an indication for urgent and non-deferrable spinal surgery.

2.3. Ethical Considerations

Since transdermal buprenorphine and oral oxycodone have already become the institution's standard-of-care management options for CLBP, formal ethics committee review by our hospital was not needed for this comparative study. Data were anonymized before analysis to preserve confidentiality for patients, as required by institutional and national data protection policies. The research complied with the Declaration of Helsinki of 1964 and its later amendments.

2.4. Treatment Protocols

Patients enrolled in the study were distributed into two groups on the basis of pharmacologic regimen as described in their clinical records. Group A patients were given a transdermal buprenorphine patch (Busette, Sandoz S.p.A., Milan, Italy) with an initial dose of 5 μg/h, with titration every week to a maximum dose of 15 μg/h as determined by pain relief and tolerability. Group B patients were given oral oxycodone/naloxone (Targin, Mundipharma International Limited, Cambridge, UK), initiating at a dose level of 5/2.5 mg twice daily, with weekly escalation to a maximum dose level of 10/5 mg twice daily as long as VAS scores were greater than or equal to 4. Treatment duration was standardized at four weeks in both groups. The rescue analgesia allowed by protocol was with acetaminophen 1000 mg, up to three times daily. In addition, use of other pain medications not listed here was barred for a duration corresponding to an agent's half-life.

Patients were scheduled at weeks 1, 2, and 4 for clinical assessments, where VAS scores and functional state as recorded through the ODI were obtained. Any incidents classified as adverse events such as nausea, vomiting, constipation, dizziness, sedation, and local skin reaction were noted.

2.5. Outcome Measures

The major outcome measure was VAS score at baseline compared to week 4, a tool widely validated for assessing pain intensity in musculoskeletal disorders [12]. The secondary outcomes were ODI, rate of dose titration, nature and frequency of adverse events, and drug compliance. The ODI is considered one of the most reliable and responsive questionnaires for evaluating functional disability in patients with low-back pain [13]. The VAS was documented on a scale ranging from 0 to 10, with 0 as no pain and 10 as worst pain imaginable. The ODI was expressed as a percentage score with higher values reflecting more disability. The severity of adverse events was assessed using a patient-reported numerical rating scale (NRS) from 0 to 10, where 0 indicated no symptom and 10 the worst imaginable severity. For analysis, scores of 1–3 were considered mild, 4–6 moderate, and 7–10 severe, in line with established grading systems such as the Patient-Reported Outcome-Common Terminology Criteria for Adverse Events (PRO-CTCAE) [14]. Symptoms without a recorded score were assumed absent or negligible and therefore not included in the analysis.

2.6. Statistical Analysis

Descriptive statistics were used to summarize baseline demographic and clinical characteristics. Results are reported as mean ± SD with 95% confidence intervals (CI). Categorical variables were expressed as counts and percentages. Patients with incomplete follow-up data at week 4 were excluded from the analysis to ensure consistency of outcome assessment (listwise deletion). Missing data were rare (<5% of cases). No imputation was performed. The final sample comprised 173 patients. Comparisons between groups were made using independent samples *t*-tests for normally distributed continuous variables and Mann–Whitney U tests for non-normally distributed variables. Chi-square or Fisher's exact tests were used for categorical variables. To assess within-group changes in VAS and ODI over time, repeated measures ANOVA was employed, followed by Bonferroni post hoc analysis. Between-group differences in the primary and secondary outcomes were assessed using analysis of covariance (ANCOVA), adjusting for baseline scores. A two-tailed *p*-value of <0.05 was considered statistically significant. All analyses were performed using IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp., Armonk, NY, USA).

3. Results

Out of 324 retrospectively examined patients, only 173 were enrolled in the study. 88 were assigned to the transdermal buprenorphine group (Group A) and 85 to the oral oxycodone/naloxone group (Group B). Baseline demographic characteristics including age, sex, and BMI were well-balanced between the groups as shown in Table 1. The mean age in Group A was 58.3 (±9.1) years, and in Group B, 57.6 (±8.9) years. For the primary outcome, Group A's VAS decreased from 7.1 (±1.0) to 2.8 (±0.7), mean difference −4.3 (95% CI: −4.6 to −4.0, $p < 0.001$). Group B's VAS decreased from 7.2 (±0.9) to 3.1 (±0.8), mean difference −4.1 (95% CI: −4.4 to −3.8, $p < 0.001$). Between-group difference at week 4: −0.3 (95% CI: −0.6 to 0.03, $p = 0.08$). At week 4, VAS reduction was numerically greater in the buprenorphine group; however, this difference did not reach statistical significance ($p = 0.08$), representing only a trend toward significance. Notably, in the first week of treatment, Group B reported slightly better pain control than Group A. This early difference is likely due to the faster onset of action of oral oxycodone/naloxone compared to the more gradual attainment of therapeutic plasma levels with transdermal buprenorphine. The ODI scores improved in both groups. In Group A, ODI decreased from 41.3% (±9.9) to 24.6% (±7.5), mean difference −16.7% (95% CI: −18.6 to −14.8, $p < 0.001$). In Group B, ODI declined from 42.1% (±10.3) to 27.1% (±8.7), mean difference −15.0% (95% CI: −16.9 to −13.1, $p < 0.001$). Between-group difference at week 4: −2.5% (95% CI: −4.9 to −0.1, $p = 0.04$). Dose escalation was required in 54.5% of patients in Group A and 68.2% in Group B. The need for upward dose titration was significantly higher in the oxycodone group ($p = 0.03$). Adverse events were more frequently reported in Group B. Nausea was observed in 21.2% of Group B patients compared to 9.1% in Group A. Constipation affected 18.8% of Group B patients and only 6.8% in Group A. Dizziness and drowsiness were also more common with oxycodone (14.1% vs. 6.8%). Local skin irritation from the patch was reported in 4.5% of patients in Group A. Three patients in Group B discontinued the treatment due to intolerable side effects, whereas only one patient discontinued in Group A.

Table 1. Demographic features.

Characteristic	Group A (Buprenorphine, n = 88)	Group B (Oxycodone/Naloxone, n = 85)	*p*-Value
Age (years), mean (SD)	58.3 (9.1)	57.6 (8.9)	0.57
Sex (Male/Female)	58/30	49/36	0.78
BMI, mean (SD)	27.3 (2.1)	26.8 (2.4)	0.54
Smoking habits (%)	49 (55.6)	45 (52.9)	0.34
Baseline VAS, mean (SD)	7.1 (1.0)	7.2 (0.9)	0.49
Baseline ODI, mean (SD)	41.3% (9.9)	42.1% (10.3)	0.58

Rescue medication use was more frequent in Group B. Rescue medication use was higher in Group A during the first week: 38.3% of buprenorphine patients required at least one dose of acetaminophen, compared to 36.5% in the oxycodone group but the difference was not statistically significant ($p = 0.07$). Over the four-week treatment period, 78.8% of Group B patients required rescue doses at least once, whereas this was observed in 53.4% of Group A ($p = 0.003$). This difference suggests a more stable and satisfactory pain control in the buprenorphine group. Summary of results were reported in Table 2. A detailed summary of adverse events by severity and by study week is now provided in Table 3, offering further insight into the tolerability profile of both regimens.

Table 2. Summary of results.

Outcome Measure	Group A (Buprenorphine, n = 88)	Group B (Oxycodone/Naloxone, n = 85)	*p*-Value
Change in VAS at Week 4	−4.3 (0.9)	−4.1 (1.0)	0.08
Mean VAS at Week 1, mean (SD)	3.8 (1.1)	4.1 (1.3)	0.06
Mean VAS at Week 4, mean (SD)	2.8 (0.7)	3.1 (0.8)	0.08
Change in ODI at Week 4 (%)	−16.7 (8.1)	−15.0 (8.9)	0.04
Mean ODI at Week 4 (%), (SD)	24.6 (7.5)	27.1 (8.7)	0.04
Dose Escalation Required (%)	54.5	68.2	0.03
Adverse Events, n (%)			
Nausea	8 (9.1)	18 (21.2)	<0.05
Constipation	6 (6.8)	16 (18.8)	<0.05
Dizziness/Drowsiness	6 (6.8)	12 (14.1)	0.07
Local Skin Irritation	4 (4.5)	0 (0.0)	<0.05
Treatment Discontinuation	1 (1.1)	3 (3.5)	0.31
Rescue Medication Use			
Used by Week 1 (%)	34 (38.6)	31 (36.5)	0.07
Used Over 4 Weeks (%)	47 (53.4)	67 (78.8)	0.03

Table 3. Adverse events by severity and study week in both groups. Values are expressed as number of patients experiencing mild, moderate, or severe adverse events at each follow-up week. Totals correspond to the cumulative incidence reported in Table 3. Data reflect documentation in clinical records; minor or transient events may be underreported.

Adverse Event	Week 1 Bupren. (M/M/S)	Week 1 Oxycod./Nal. (M/M/S)	Week 2 Bupren. (M/M/S)	Week 2 Oxycod./Nal. (M/M/S)	Week 3 Bupren. (M/M/S)	Week 3 Oxycod./Nal. (M/M/S)	Week 4 Bupren. (M/M/S)	Week 4 Oxycod./Nal. (M/M/S)
Nausea	3/1/0	6/2/0	2/1/0	4/2/0	1/0/0	3/0/0	1/0/0	2/0/0
Constipation	2/1/0	5/1/0	2/0/0	4/1/0	1/0/0	3/0/0	1/0/0	3/0/0
Dizziness/Drowsiness	2/1/0	4/1/0	2/0/0	3/1/0	1/0/0	2/0/0	0/0/0	1/0/0
Local Irritation	1/0/0	0/0/0	2/0/0	0/0/0	1/0/0	0/0/0	0/0/0	0/0/0

4. Discussion

4.1. Background

CLBP remains one of the most prevalent and debilitating musculoskeletal conditions worldwide, representing a significant cause of disability and diminished quality of life [15]. Even though the natural history of some cases suggests partial symptom improvement over time, for many individuals the condition persists despite guideline-based conservative management [15,16]. Such persistence can lead to chronic functional impairment, substantial psychological distress, and notable socioeconomic repercussions, including loss of work productivity and increased health-care utilization [15,16]. For patients in whom first-line interventions—such as non-steroidal anti-inflammatory drugs (NSAIDs), structured physiotherapy, and certain adjuvant pharmacological treatments like antidepressants or anticonvulsants—fail to produce adequate relief, clinicians may escalate to opioid therapy [17]. While opioids are widely recognized for their potent analgesic properties, their use is accompanied by well-documented safety concerns, including the potential for misuse, dependence, tolerance, and a range of adverse effects that may offset their benefits [17].

Within this therapeutic landscape, transdermal buprenorphine and oral oxycodone/naloxone are frequently considered viable options for more severe or refractory cases [18]. Despite their shared classification as opioid analgesics, they differ substantially in their pharmacodynamic and pharmacokinetic characteristics, as well as in their clinical tolerability

profiles [19]. Gordon et al. [20] demonstrated that the buprenorphine transdermal system is an effective pharmacological option for managing chronic low-back pain. Specifically, the significant reduction in pain intensity and the favorable tolerability profile observed in our cohort mirror the positive outcomes reported in their randomized controlled trial and subsequent open-label extension [20]. A Phase 3 randomized study by Stainer et al. demonstrated the efficacy and safety of a buprenorphine transdermal system in patients with chronic low-back pain, finding a 20 mcg/h dose to be significantly more effective than a lower dose [21].

The present study was designed to explore these differences in a real-world clinical setting, focusing specifically on comparative efficacy and tolerability in a population with CLBP that had proven resistant to earlier treatment strategies.

4.2. Our Findings

Our retrospective cohort findings demonstrate that both transdermal buprenorphine and oral oxycodone/naloxone produced meaningful reductions in pain intensity and functional disability over a four-week observation period. This aligns with prior research confirming that, in appropriately selected patients, opioid therapy can offer short-term improvements in pain and function [9]. However, subtle but potentially important distinctions emerged between the two regimens, particularly in relation to the trajectory of pain relief, functional restoration, side-effect burden, and the pattern of rescue medication usage.

4.2.1. Pain Relief

The degree of pain relief achieved, as measured by VAS scores, was substantial in both treatment groups. While the greater reduction observed in the buprenorphine group did not reach conventional statistical significance ($p = 0.08$), the numerical difference is arguably of clinical interest, especially when interpreted alongside the results for functional improvement. In contrast, the ODI improvement in the buprenorphine group did reach statistical significance ($p = 0.04$), suggesting that the observed benefits extended beyond analgesia to include a more meaningful restoration of daily living capabilities [9]. This distinction is clinically relevant, as pain intensity and functional capacity do not always improve in parallel; the ability to resume activities of daily living is often a more tangible and valuable outcome for patients than numerical reductions in pain scores alone.

A closer examination of the week-by-week progression revealed an interesting divergence in onset patterns. Patients receiving oxycodone/naloxone reported slightly faster initial pain relief, particularly in the first week of therapy. This is pharmacologically plausible, as oral oxycodone is rapidly absorbed and reaches peak plasma concentrations quickly, enabling a swift analgesic effect [9,22]. In contrast, transdermal buprenorphine relies on gradual systemic absorption through the skin, leading to a more measured rise in plasma concentration and a correspondingly slower onset of maximal analgesic benefit [9,20]. This pharmacokinetic characteristic likely explains the more frequent need for rescue medication in the buprenorphine group during the initial week of treatment.

However, by the second week, this dynamic shifted. Once therapeutic plasma concentrations of buprenorphine were established, patients tended to experience a more consistent and sustained analgesic effect, with fewer episodes of breakthrough pain requiring additional medication [9,23]. This stability persisted for the remainder of the observation period, ultimately resulting in a lower overall reliance on rescue analgesia in the buprenorphine group. From a patient-centered perspective, this consistency in pain control is important—it can reduce the psychological burden of unpredictable symptom flares and may improve treatment satisfaction and adherence [9,23].

4.2.2. Tolerability

Tolerability is another cornerstone of effective pain management, particularly in chronic conditions that necessitate ongoing therapy. Our analysis showed a clear advantage for buprenorphine in this regard. Adverse effects classically associated with opioid therapy—such as nausea, constipation, dizziness, and sedation—were reported less frequently among patients using the transdermal formulation [20]. This pattern is consistent with buprenorphine's partial μ-opioid receptor agonist activity, which allows for robust analgesia while producing a ceiling effect on certain adverse effects, most notably respiratory depression [22]. By contrast, oxycodone, a full μ-opioid receptor agonist, lacks this pharmacological safeguard and is therefore more prone to producing dose-dependent adverse events [9,22].

Better tolerability has practical implications beyond mere comfort. It can reduce the likelihood of therapy discontinuation, decrease the need for symptomatic management of side effects (such as laxatives for constipation or antiemetics for nausea), and support higher adherence rates [9]. In real-world clinical practice, adherence is a decisive factor in achieving sustained pain relief and functional improvement. The fewer barriers patients encounter in tolerating their medication, the more likely they are to maintain it long enough to derive full benefit.

4.2.3. Dose Escalation

The pattern of dose escalation also warrants attention. Our findings suggest that oxycodone/naloxone recipients required upward dose adjustments more frequently than those on buprenorphine. This may reflect a faster development of pharmacological tolerance to oxycodone, a phenomenon well-documented with full opioid agonists [24]. In contrast, buprenorphine's unique receptor pharmacology may confer greater stability over time, slowing the emergence of tolerance and reducing the need for dose escalation [24]. This is particularly advantageous in long-term management, where maintaining efficacy without escalating risk is a persistent challenge.

4.3. Pharmacological and Clinical Implications

Buprenorphine's pharmacological profile offers additional theoretical benefits that may be relevant in chronic pain populations. Its κ-opioid receptor antagonism has been proposed to mitigate certain negative mood states and possibly counteract opioid-induced hyperalgesia. Moreover, its ceiling effect on respiratory depression makes it a safer option for populations at increased risk, such as elderly patients or those with chronic obstructive pulmonary disease or sleep apnea [8]. While our study was not designed to directly measure these endpoints, the existing literature supports their clinical plausibility and underscores the importance of tailoring opioid selection to the specific vulnerabilities of the patient [8].

From a practical standpoint, the mode of administration also matters. The transdermal patch offers convenience for patients with dysphagia, gastrointestinal disorders that may impair absorption, or those on complex medication regimens where simplifying dosing can enhance adherence [24]. It also facilitates steady-state plasma levels without the peaks and troughs associated with multiple daily oral dosing [19]. In contrast, oral oxycodone/naloxone requires more frequent administration and carries the added consideration of gastrointestinal tolerability, even with the inclusion of naloxone to mitigate constipation [24].

The broader implications of these findings extend to prescribing practices in CLBP management. While opioids should be used judiciously and typically reserved for cases unresponsive to other modalities [17], our results suggest that transdermal buprenorphine

may offer a more favorable balance between efficacy and safety, particularly in opioid-naïve individuals or those with comorbidities that heighten their risk from full opioid agonists [24]. This is not to suggest that buprenorphine is devoid of risks; it remains a controlled substance with abuse potential and must be prescribed with careful patient selection, monitoring, and education [24]. However, in appropriately selected patients, it may represent a safer long-term choice.

It is also worth noting that our study adds to the relatively limited pool of real-world comparative data on these two specific regimens in CLBP [9,18]. Most prior research has either examined each drug in isolation or in comparison with placebo, rather than directly against one another [18]. By focusing on head-to-head outcomes, we provide a more clinically relevant framework for decision-making, though the retrospective nature of the study and the relatively short observation period necessitate cautious interpretation [9,21]. These findings support a role for buprenorphine as a first-line opioid option in carefully selected CLBP patients requiring escalation beyond non-opioid therapy [24].

4.4. Limitations and Future Directions

While this study provides valuable insights into the comparative effectiveness and tolerability of transdermal buprenorphine and oral oxycodone/naloxone in chronic low-back pain, several limitations must be considered. First, the retrospective design precludes causal inference and depends on the accuracy of medical records. Treatment allocation was not randomized but based on physicians' judgment and patient characteristics, which may have introduced selection bias. Adverse events were only documented if noted in clinical files, meaning mild or transient side effects may have been underreported, potentially underestimating tolerability issues. Second, the absence of a control group receiving placebo or non-opioid analgesics prevents us from distinguishing drug-specific effects from placebo response, regression to the mean, or natural symptom variation. Moreover, since participants had already failed NSAIDs and physiotherapy, our findings may not apply to patients earlier in their treatment pathway. Third, the follow-up period of four weeks was sufficient for short-term assessment of pain, function, and tolerability, but too brief to evaluate long-term outcomes such as tolerance, dependence, or sustained functional benefit. Future prospective studies with longer observation are required to clarify these aspects. Another limitation concerns generalizability. The sample was drawn from a single institution, after comprehensive diagnostic imaging, and excluded patients with psychiatric comorbidities, substance abuse, or significant organ dysfunction. While these criteria improved internal validity, they also restrict applicability to the broader chronic pain population, particularly in primary care settings. Finally, this analysis compared only two opioid regimens. Other pharmacologic or multidisciplinary approaches were not included, limiting the conclusions to this specific head-to-head comparison. In summary, our results suggest that transdermal buprenorphine offers a favorable short-term balance of efficacy and tolerability compared with oxycodone/naloxone. However, these conclusions should be interpreted cautiously. Prospective, randomized, multicenter studies with longer follow-up and broader inclusion criteria are needed to confirm these findings and to evaluate long-term safety and patient-centered outcomes.

5. Conclusions

In this retrospective cohort of patients with CLBP unresponsive to NSAIDs and physiotherapy, both transdermal buprenorphine and oral oxycodone/naloxone produced clinically meaningful short-term reductions in pain and disability over four weeks. While our findings suggest that transdermal buprenorphine may offer certain tolerability and

adherence advantages, these results should be interpreted as short-term observations and no conclusions can be drawn regarding long-term management.

Transdermal buprenorphine, however, was associated with superior tolerability, reduced requirement for dose escalation, and substantially lower cumulative use of rescue analgesics. These practical advantages—together with the pharmacologic properties of buprenorphine (partial μ-agonism and κ-antagonism) and steady transdermal deliver—support its consideration as a primary opioid option in appropriately selected patients with CLBP, particularly where long-term tolerability and maintenance analgesia are priorities.

Future research should prioritize prospective randomized controlled trials comparing transdermal buprenorphine and full μ-agonists over longer time horizons (months to years), with comprehensive evaluation of addiction-related outcomes, objective functional endpoints, patient-reported quality of life, health-economic analyses, and stratification by patient subgroups (older adults, those with pulmonary disease, prior opioid exposure, or psychiatric comorbidity). Additional mechanistic studies examining buprenorphine's impact on opioid-induced hyperalgesia, mood, and sleep in CLBP would further elucidate potential advantages. Finally, research into optimal strategies for bridging the initial latency to steady-state transdermal concentrations (for example, short-term adjunctive analgesia or different titration algorithms) could improve early symptom control without sacrificing the long-term tolerability benefits observed here.

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Informed Consent Statement: Informed consent for the scientific use of anonymized clinical data was obtained in compliance with institutional regulations and the guidelines of the Italian Data Protection Authority. All patient data were fully anonymized to safeguard confidentiality.

Data Availability Statement: The datasets generated and/or analyzed during the current study are not publicly available due to institutional data protection policies but are available from the corresponding author upon reasonable request.

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References

1. Gilmore, C.A.; Deer, T.R.; Desai, M.J.; Li, S.; DePalma, M.J.; Cohen, S.P.; Swan, B.D.; McGee, M.J.; Boggs, J.W. Four-Year Follow-Up from a Prospective, Multicenter Study of Percutaneous 60-Day Peripheral Nerve Stimulation for Chronic Low Back Pain. *Pain Ther.* **2025**, *14*, 1103–1115. [CrossRef]
2. Hoy, D.; Bain, C.; Williams, G.; March, L.; Brooks, P.; Blyth, F.; Woolf, A.; Vos, T.; Buchbinder, R. A systematic review of the global prevalence of low back pain. *Arthritis Rheumatol.* **2012**, *64*, 2028–2037. [CrossRef]

3. Perna, A.; Ricciardi, L.; Barone, G.; Tamburrelli, F.C.; Proietti, L.; Pola, E. Medical management of acute non-specific low back pain: Comparison of different medical treatments, one center's retrospective analysis. *J. Biol. Regul. Homeost. Agents* **2019**, *32* (Suppl. 1), 121–129.
4. Ricciardi, L.; Sturiale, C.L.; Pucci, R.; Reale, G.; Stifano, V.; Izzo, A.; Perna, A.; Proietti, L.; Forcato, S.; Perla, K.M.R.; et al. Patient-Oriented Aesthetic Outcome After Lumbar Spine Surgery: A 1-Year Follow-Up Prospective Observational Study Comparing Minimally Invasive and Standard Open Procedures. *World Neurosurg.* **2019**, *122*, e1041–e1046. [CrossRef]
5. Chou, R.; Qaseem, A.; Snow, V.; Casey, D.; Cross, J.T., Jr.; Shekelle, P.; Owens, D.K.; Clinical Efficacy Assessment Subcommittee of the American College of Physicians; The American College of Physicians/American Pain Society Low Back Pain Guidelines Panel. Diagnosis and treatment of low back pain: A joint clinical practice guideline from the American College of Physicians and the American Pain Society. *Ann. Intern. Med.* **2007**, *147*, 478–491; Correction in *Ann. Intern Med.* **2008**, *148*, 247–248. https://doi.org/10.7326/0003-4819-148-3-200802050-00020. [CrossRef]
6. Rauck, R.L.; Potts, J.; Xiang, Q.; Tzanis, E.; Finn, A. Efficacy and tolerability of buccal buprenorphine in opioid-naive patients with moderate to severe chronic low back pain. *Postgrad. Med.* **2016**, *128*, 1–11. [CrossRef]
7. Chou, R.; Fanciullo, G.J.; Fine, P.G.; Adler, J.A.; Ballantyne, J.C.; Davies, P.; Donovan, M.I.; Fishbain, D.A.; Foley, K.M.; Fudin, J.; et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J. Pain* **2009**, *10*, 113–130.e22. [CrossRef]
8. Tiemstra, J.D. Common Questions About Buprenorphine Treatment for Opioid Use Disorder. *Am. Fam. Physician* **2025**, *111*, 330–336. [PubMed]
9. Ahmad, A.; Khan, K.A.; Hamid, E.; Nisar, M.F.; Rehmat, A. Effectiveness and Safety of Transdermal Buprenorphine for Acute Postoperative Pain Management Following Mandibular Resection: A Prospective Observational Study. *Cureus* **2025**, *17*, e79634. [CrossRef] [PubMed]
10. Hwang, C.J.; Chung, S.S.; Lee, K.-Y.; Lee, J.H.; Moon, S.-H.; Kim, J.-H.; Cho, K.-J.; Ahn, J.-S.; Kim, D.-S.; Park, Y.-S.; et al. Analgesic Efficacy and Safety of Prolonged-Release Oxycodone/Naloxone in Korean Patients with Chronic Pain from Spinal Disorders. *Clin. Orthop. Surg.* **2018**, *10*, 33–40. [CrossRef] [PubMed]
11. Cuschieri, S. The STROBE guidelines. *Saudi J. Anaesth.* **2019**, *13*, 31–34. [CrossRef]
12. Chiarotto, A.; Maxwell, L.J.; Ostelo, R.W.; Boers, M.; Tugwell, P.; Terwee, C.B. Measurement Properties of Visual Analogue Scale, Numeric Rating Scale, and Pain Severity Subscale of the Brief Pain Inventory in Patients With Low Back Pain: A Systematic Review. *J. Pain* **2019**, *20*, 245–263. [CrossRef]
13. Chiarotto, A.; Maxwell, L.J.; Terwee, C.B.; Wells, G.A.; Tugwell, P.; Ostelo, R.W. Roland-Morris Disability Questionnaire and Oswestry Disability Index: Which Has Better Measurement Properties for Measuring Physical Functioning in Nonspecific Low Back Pain? Systematic Review and Meta-Analysis. *Phys. Ther.* **2016**, *96*, 1620–1637. [CrossRef]
14. Basch, E.; Reeve, B.B.; Mitchell, S.A.; Clauser, S.B.; Minasian, L.M.; Dueck, A.C.; Mendoza, T.R.; Hay, J.; Atkinson, T.M.; Abernethy, A.P.; et al. Development of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). *JNCI J. Natl. Cancer Inst.* **2014**, *106*, dju244. [CrossRef]
15. Perna, A.; Fumo, C.; Proietti, L.; Bocchi, M.B.; Zirio, G.; Genitiempo, M.; Meluzio, M.C.; Tamburrelli, F.C.; Cerciello, S.; Santagada, D.A. The importance of telemedicine and home therapy during COVID-19 pandemic: The role of semirigid corset in acute low back pain. *Minerva Orthop.* **2021**, *72*, 526–532. [CrossRef]
16. Caruana, C.; Grech, S.; Cuschieri, S. Low back pain: The forgotten public health epidemic. *Future Healthc. J.* **2025**, *12*, 100233. [CrossRef]
17. Andresen, A.K.; Carreon, L.Y.M.; Bech, R.; Bjarkam, C.R.; Bruun, C.; Caspersen, J.; Dons, K.; Jørgensen, L.M.; Rasmussen, M.; Nielsen, M.; et al. Perioperative Opioid Consumption in Patients who Undergo Surgery due to Spine Related Pain. A Danish Nationwide Cohort Study. *Spine* **2024**, *50*, E370–E374. [CrossRef] [PubMed]
18. Hale, M.; Urdaneta, V.; Kirby, T.; Xiang, Q.; Rauck, R. Long-term safety and analgesic efficacy of buprenorphine buccal film in patients with moderate-to-severe chronic pain requiring around-the-clock opioids. *J. Pain Res.* **2017**, *10*, 233–240. [CrossRef]
19. Webster, L.R.; Cater, J.; Smith, T. Pharmacokinetics of Buprenorphine Buccal Film and Orally-administered Oxycodone in a Respiratory Study: An Analysis of Secondary Outcomes from a Randomized Controlled Trial. *Pain Ther.* **2022**, *11*, 817–825. [CrossRef] [PubMed]
20. Gordon, A.; Callaghan, D.; Spink, D.; Cloutier, C.; Dzongowski, P.; O'mAhony, W.; Sinclair, D.; Rashiq, S.; Buckley, N.; Cohen, G. Buprenorphine transdermal system in adults with chronic low back pain: A randomized, double-blind, placebo-controlled crossover study, followed by an open-label extension phase. *Clin. Ther.* **2010**, *32*, 844–860. [CrossRef] [PubMed]
21. Steiner, D.; Munera, C.; Hale, M.; Ripa, S.; Landau, C. Efficacy and safety of buprenorphine transdermal system (BTDS) for chronic moderate to severe low back pain: A randomized, double-blind study. *J. Pain* **2011**, *12*, 1163–1173. [CrossRef] [PubMed]
22. Sakae, M. Buprenorphine: Opioid Agonist-Antagonist for Refractory Pain of Sickle Cell Disease Patients During Hematopoietic Stem Cell Transplant, Uncontrolled By Full-Agonist Opioids. *J. Opioid Manag.* **2024**, *20*, B14. [CrossRef] [PubMed]

23. Feng, W.; Wang, Y.; Ran, F.; Mao, Y.; Zhang, H.; Wang, Q.; Lin, W.; Wang, Z.; Hu, J.; Liao, W.; et al. The effectiveness and safety of the rapid titration strategy of background controlled-release oxycodone hydrochloride for patients with moderate-to-severe cancer pain: A retrospective cohort study. *Front. Med.* **2022**, *9*, 918468. [CrossRef] [PubMed]
24. Londhe, S.B.; Patwardhan, M.; Shah, R.V.; Desouza, C.; Oak, M.; Antao, N.A. Comparison of the efficacy and safety of transdermal buprenorphine patch to conventional analgesics after operative fixation of extra capsular fracture of proximal femur. *Injury* **2024**, *55* (Suppl. 2), 111395. [CrossRef]