doi.org/10.36721/PJPS.2026.39.11.318.1

Real-world patterns of analgesic combination therapy and their associations with pain intensity and treatment modification in patients with chronic non-cancer pain: A retrospective observational study

Linlin Chao, Weixing Li, Jinsen Zhang and Zhenyu Cai*
Pain Department, The First Affiliated Hospital of Xiamen University, Xiamen 361000, Fujian Province, China

Abstract: **Background**: Chronic non-cancer pain (CNCP) is highly prevalent and often requires analgesic combination therapy due to its complex mechanisms. However, real-world evidence on how different combination regimens correlate with pain relief and treatment modification remains limited, which hampers optimal multimodal analgesia selection. **Objectives**: To explore real-world analgesic combination patterns in CNCP, analyze their associations with pain intensity changes and regimen adjustments and provide evidence for individualized multimodal analgesia. **Methods**: This retrospective study included 120 CNCP patients (Jan 2022 to Jan 2024) categorized into three regimens: Dual (NSAIDs + acetaminophen, n=42), Opioid (weak opioid + adjuvant, n=38) and Triple (NSAIDs + opioid + adjuvant, n=40). Numerical Rating Scale (NRS) scores, therapy duration, regimen adjustments and adverse reactions were extracted. Multiple linear regression and binary logistic regression were used to identify factors associated with pain relief and treatment modification. **Results**: The Triple group achieved the highest pain-relief rate (77.5%) compared with the Opioid (63.2%) and Dual (50.0%) groups (P<0.05). The treatment modification rate was highest in the Dual group (45.2%, mainly escalation; P<0.05). Adverse reactions were more frequent in the Triple group than in the Dual group (P<0.05), but no serious events occurred. Regression analyses identified Triple therapy (B=0.455, 95% CI: 0.260–0.649, P<0.001) and baseline NRS (B=0.607, 95% CI: 0.491–0.723, P<0.001) as independent factors for greater pain relief. Triple therapy (OR=0.256, 95% CI: 0.090–0.729, P=0.011) and longer baseline pain duration (OR=0.917, 95% CI: 0.860–0.978, P=0.009) were independent protective factors against treatment modification. **Conclusion**: CNCP patients exhibit distinct patterns of analgesic combination. Triple therapy was associated with better pain relief persistence and fewer adjustments but higher adverse reaction risks. Therapy selection should be stratified by pain phenotype and patients with moderate-to-severe pain may benefit from early standardized combination therapy, which was linked to fewer subsequent regimen adjustments.

Keywords: Analgesics; Chronic pain; Combination; Drug therapy, Pain management; Pain measurement; Retrospective studies

Submitted on 24-04-2026 – Revised on 05-06-2026 – Accepted on 15-06-2026

INTRODUCTION

Chronic non-cancer pain (CNCP) refers to a pain syndrome caused by non-malignant factors that lasts for more than 3 months. The global prevalence is about 20% - 30%, which seriously affects the quality of life of patients and creates a huge social and economic burden (Mills *et al*., 2019). The etiology of CNCP is complex, covering various types of diseases such as osteoarthritis, lower back pain, neuropathic pain, fibromyalgia syndrome, etc. Its pathological and physiological mechanisms involve multiple levels such as peripheral sensitization, central sensitization, inflammatory response and neuroplasticity changes (Woolf, 2011). Due to the difficulty of effectively controlling CNCP with a single analgesic drug, multimodal analgesia has become a clinical consensus. By combining analgesics with different mechanisms of action, the goal is to achieve synergistic efficacy, reduce single drug doses and related adverse reactions. Contemporary guidelines, including the 2022 Centers for Disease Control and Prevention Clinical Practice Guideline for Prescribing Opioids for Pain (Dowell *et al*., 2022) and the 2021 National Institute for Health and Care Excellence guideline NG193 (Carville *et al*., 2021), recommend a multimodal and multidisciplinary approach to pain management that prioritizes nonpharmacologic and nonopioid pharmacologic therapies, with opioids reserved for cases where benefits are anticipated to outweigh risks. The European Pain Federation (EFIC) similarly emphasizes that opioids should not be prescribed as first-line therapy for chronic primary pain and should serve only as second- or third-line treatment in chronic secondary pain, after optimization of multimodal non-opioid strategies (Hauser *et al*., 2021).

By combining analgesics with different mechanisms of action, the goal is to achieve synergistic efficacy and reduce single-drug doses and related adverse reactions (Kehlet and Dahl, 1993). The clinical management of CNCP has long faced core challenges such as inadequate efficacy, high incidence of adverse drug reactions and significant heterogeneity in individual responses. In this context, the combination therapy of analgesics has gradually evolved from empirical attempts to systematic strategies based on neurobiological mechanisms and its

**Corresponding author:* e-mail: czy168200202@hotmail.com

real-world application patterns and clinical effects urgently require empirical analysis based on large-scale clinical data. Multiple studies have confirmed the efficacy of combination therapy: the combination of sustained-release hydrocodone and pregabalin can significantly reduce NRS scores, with a treatment response rate of 78.3% (Gatti *et al*., 2011); OROS ®. At the 6-month follow-up, the NRS score of the combination of hydromorphone and pregabalin decreased by 4.2 points and the overall patient satisfaction reached 65.4% (Dauri *et al*., 2014). These data indicate that the synergy between opioid drugs and calcium channel modulators is not simply a superposition, but rather through targeting different pathological processes: opioids inhibit ascending pain conduction, while pregabalin directly intervenes in central sensitization, the core driving mechanism of CNCP, by binding to voltage-gated calcium channel α2-δ subunits to reduce the release of excitatory neurotransmitters (such as glutamate and substance P) in the spinal dorsal horn (Hauser *et al*., 2021).

Nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen are first-line treatment options for CNCP, exerting analgesic effects by inhibiting peripheral prostaglandin synthesis (Moore *et al*., 2015a). However, the analgesic effect of NSAIDs has a ceiling effect and long-term use is associated with gastrointestinal adverse reactions, cardiovascular risk and renal dysfunction (Scarpignato *et al*., 2015, Bally *et al*., 2017). For patients with moderate to severe pain components, it is often necessary to combine weak opioid drugs or adjuvant analgesics, such as gabapentin, tricyclic antidepressants (Dworkin *et al*., 2010). Gabapentin and pregabalin, as calcium channel α2-δ ligands, have shown good efficacy in the treatment of neuropathic pain by regulating voltage-dependent calcium channels to reduce neurotransmitter release (Moore *et al*., 2009). For chronic low back pain with both nociceptive and neuropathic components, a eutectic formulation of tramadol combined with celecoxib is commonly used in clinical practice. The summary analysis of phase III clinical trials confirms that this combination has a faster onset of action and higher peak pain relief in acute moderate to severe pain and the incidence of gastrointestinal side effects is significantly lower than that of tramadol alone (Langford *et al*., 2024). The complementary drug logic of this mechanism is the essence of multimodal analgesia, which is thought to achieve synergistic effect through multi-target action, reducing the dosage of a single drug and related adverse reactions (Gilron *et al*., 2013; Dale and Stacey, 2016).

Although combination analgesic therapy has theoretical advantages, there remains a lack of systematic research on its practical models and their association with real-world clinical outcomes. Previous randomized controlled trials (RCTs) have mostly focused on the short-term efficacy evaluation of specific drug combinations, while in actual clinical practice, patients' medication patterns are more complex, involving dynamic adjustments of multiple drug combinations (Gilron *et al*., 2015). In addition, the duration of combination therapy, frequency of treatment plan adjustments and their influencing factors have been less reported in Real World Evidence (RWE) studies. The adjustment of treatment plans includes dose titration, drug replacement, plan upgrade or downgrade, etc., reflecting the dynamic changes in pain control and the complexity of clinical decision-making (Deyo *et al*., 2013; Eriksen *et al*., 2006; Busse *et al*., 2018; Cohen *et al*., 2021). The aim of this study is to retrospectively analyze the analgesic combination therapy patterns of CNCP patients in a real-world clinical setting, explore the associations between different combination regimens and changes in pain intensity and treatment regimen adjustments and provide evidence-based support for optimizing individualized multimodal analgesic strategies for CNCP.

MATERIALS AND METHODS

Study subjects

This retrospective clinical observational study had its data extracted and analyzed by researchers independent of patient treatment. Via the electronic medical record system, 120 eligible CNCP patients admitted to the First Affiliated Hospital of Xiamen University's Pain Departments (Jan 2022 to Jan 2024) were identified. Demographic, clinical, analgesic treatment and follow-up data were extracted; all patients received ≥6 weeks of combined analgesia. Patients were categorized into Dual (n=42), Opioid (n=38) and Triple (n=40) groups by regimen (Fig. 1).

Data extraction and coding: Patients were identified using the hospital's electronic medical record (EMR) system. Diagnoses were extracted based on documented physician-confirmed clinical diagnoses (osteoarthritis, low back pain, neuropathic pain, etc.) rather than ICD-10 codes, due to the single-center EMR structure. Analgesic medications were classified according to the hospital formulary and pharmacological categories: NSAIDs (celecoxib, loxoprofen, ibuprofen, diclofenac), weak opioids (tramadol, codeine, dihydrocodeine), and adjuvants (pregabalin, gabapentin, duloxetine, amitriptyline). All prescriptions were verified by manual chart review to ensure accuracy.

Inclusion criteria

(1) Age ≥ 18 years old; (2) History of chronic pain ≥ 3 months; (3) Accepted the combined analgesic treatment plan; (4) Completed clinical data, including pain assessment records, medication records and follow-up data; (5) The duration of combination therapy is ≥ 6 weeks.

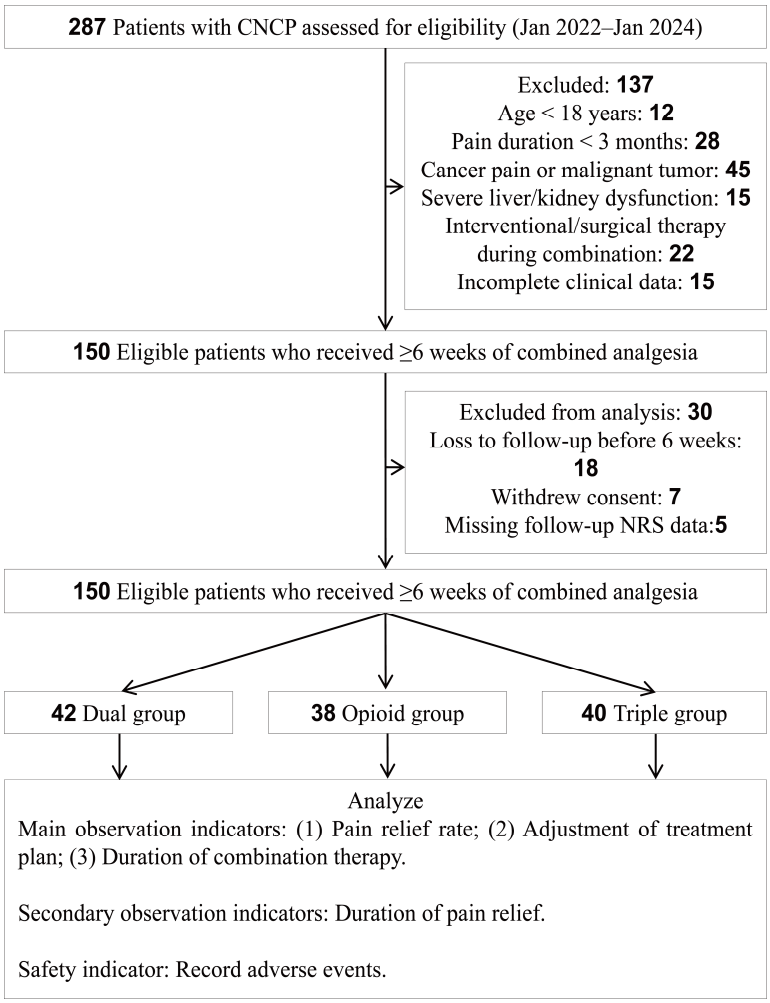

Fig. 1: Research flowchart.

Exclusion criteria

(1) History of cancer pain or malignant tumors; (2) Acute pain or postoperative pain; (3) Severe liver and kidney dysfunction (Child Pugh grade C or eGFR<30 mL/min); (4) Pregnant or lactating women; (5) History of drug abuse or addiction; (6) Received interventional therapy or surgical treatment during combination therapy.

Ethical statement

This study strictly adheres to the principles of the Helsinki Declaration (Wen *et al*., 2025) and was approved by the Ethics Committee of The First Affiliated Hospital of Xiamen University (approval No. 2026-083, dated April 22, 2026). Written informed consent was obtained from all participants prior to enrollment. All patient data were anonymized to ensure privacy.

Sample size estimation

Because this study was retrospective, sample size was determined by available records. A retrospective power assessment using G*Power 3.1.9.7 (Kim *et al*., 2017) for the primary outcome—pain relief rate (≥50% NRS reduction). The assumed medium effect size (Cohen's f = 0.30) was conservatively derived from prior combination-versus-monotherapy studies in neuropathic pain (Hanna *et al*., 2008, Gilron *et al*., 2009), acknowledging that comparing three active regimens in mixed-etiology CNCP would yield smaller differences. A total of 111 subjects (37/group) is required for f = 0.30, α = 0.05, power = 0.80. This cohort (n = 120) achieved 83.6% power. The observed effect size (f ≈ 0.23) confirmed the previously conservative assumption.

Grouping method

Patients were categorized into three groups based on their actual clinical analgesic combination prescriptions:

Dual group (n=42): NSAIDs included celecoxib (100-200 mg bid), loxoprofen (60 mg tid), ibuprofen (200-400 mg tid), or diclofenac (50 mg bid). Acetaminophen was given at 0.5-1.0 g tid (maximum 3 g/day).

Opioid group (n=38): Weak opioids included tramadol (50–100 mg qid, immediate or sustained release), codeine (30–60 mg qid), or dihydrocodeine/paracetamol fixed combinations. Adjuvants included pregabalin (75–150 mg bid), gabapentin (300–900 mg tid), duloxetine (30–60 mg qd), or amitriptyline (10–25 mg qhs). Only one adjuvant was used per patient.

Triple group (n=40): Triple combination of NSAIDs, opioids and adjuvant analgesics, formed by adding NSAIDs to the Opioid group regimen for multi-target analgesia covering peripheral inflammation, central conduction and neuropathic pain.

Heterogeneity within groups: Different drugs within the same category (e.g., various NSAIDs or adjuvants) were pooled due to small subgroup sizes. Dose titration was not standardized. This heterogeneity may affect reproducibility and is further discussed in the limitations section.

For patients with regimen escalation (e.g., from Dual to Triple) during the observation period, the upgraded regimen was included in the analysis and all such adjustment events were documented. Treatment modification was defined as a composite outcome comprising dose escalation/reduction (⩾25%), drug substitution (within the same class), regimen upgrade (increasing the number of drug classes), or regimen downgrade (reducing the number of drug classes). These events have distinct clinical implications; they were pooled into a single binary outcome to maintain statistical power given the limited sample size for individual event types.

Justification for grouping strategy: The adjuvant category (pregabalin, gabapentin, duloxetine, amitriptyline) comprises agents commonly used for neuropathic pain and central sensitization in CNCP clinical practice. Despite distinct primary mechanisms, they are routinely prescribed as interchangeable "adjuvant analgesics" when multimodal therapy is indicated. Similarly, the opioid group included only weak opioids (tramadol, codeine, dihydrocodeine) at standard analgesic dosages, which have comparable efficacy and safety profiles in real-world settings.

Observation indicators

Main observation indicators

(1) *Pain relief rate*: Defined as the proportion of patients with a ≥50% reduction in Numerical Rating Scale (NRS) scores (Hjermstad *et al*., 2011, Farrar *et al*., 2001) from baseline at 6 weeks post-treatment. The 0–10 NRS scale denotes no pain (0) to severe pain (10); NRS data were extracted at baseline and 6 weeks post-treatment.

(2) *Treatment regimen adjustment*: Defined as any of the following changes identified during the observation period: (1) ≥25% dose escalation/reduction of any drug; (2) drug replacement (discontinuation and substitution of same-class agents); (3) regimen upgrade (increased drug classes, e.g., dual to triple); (4) regimen downgrade (reduced drug classes, e.g., triple to dual). Adjustment details were verified comprehensively via prescription, outpatient and follow-up records.

Secondary observation indicators

(1) *Combined analgesic therapy efficacy*: NRS score absolute change (baseline NRS minus 6-week NRS) and relative reduction rate (absolute change/baseline NRS ×100%) were extracted for efficacy evaluation.

(2) *Analgesic regimen duration*: This was defined as the time interval from regimen initiation to the first occurrence of: (1) regimen adjustment; (2) study conclusion (6-week observation); (3) loss to follow-up or withdrawal. Data were documented weekly.

(3) *Pain relief duration*: For patients with ≥50% NRS reduction, this referred to the time from first meeting the criterion to pain rebound (NRS reduction <50%) or the end of extended follow-up (up to 12 weeks), whichever occurred first. The 6-week primary endpoint was used for analyses of pain relief rate and NRS change.

(4) *Treatment adjustment rate and type distribution*: Adjustment rates were calculated for each group and adjustment characteristics were described by specific types (dose adjustment, drug replacement, regimen upgrade, regimen downgrade) based on retrospective data sorting.

Safety indicators

Safety assessment was based on documented adverse reactions (ARs) recorded in medical charts and follow-up notes. ARs were coded using the Medical Dictionary for Regulatory Activities system (Brown *et al*., 1999). Due to the retrospective nature, the following information was not systematically available: severity grading (e.g., Common Terminology Criteria for Adverse Events criteria), causality assessment (e.g., definite, probable and possible) and whether patients experienced multiple events simultaneously. No serious adverse reaction events were identified in this cohort.

Statistical analysis

Data analyses were performed via SPSS 25.0. Normality was assessed using the Kolmogorov-Smirnov test with Q-Q plots, and homogeneity of variances was assessed using Levene's test. Normally distributed continuous data were compared across three groups using one-way ANOVA, followed by Tukey HSD post hoc test for pairwise comparisons when the overall F-test was significant ($P<0.05$). Categorical data were analyzed using the chi-square test, with Bonferroni correction applied for multiple pairwise comparisons where appropriate. Count data as n (%) with the chi-square test applied. Multiple linear regression was conducted with pain relief degree as the dependent variable to identify independent effects of analgesic regimens and baseline pain characteristics on pain relief. Binary logistic regression was performed with treatment regimen adjustment as the dependent variable to explore its influencing factors. As a sensitivity analysis, a one-way analysis of covariance (ANCOVA) was performed with baseline NRS as a covariate to compare 6-week NRS among the three groups, followed by Bonferroni-corrected pairwise comparisons.

Table 1: Baseline characteristics [mean ±SD, n (%)].

Variables	Dual group (n=42)	Opioid group (n=38)	Triple group (n=40)	F/χ^2	P
Age (years)	56.3±4.8	58.1±5.5	57.6±5.2	1.288	0.280
Female	24 (57.1)	21 (55.3)	23 (57.5)	0.046	0.977
BMI (kg/m²)	25.4±3.6	26.1±4.2	25.8±3.9	0.248	0.781
Pain duration (months)	18.5±5.3	21.2±8.6	19.8±7.4	1.495	0.229
Baseline NRS score	5.8±1.2	6.2±1.4	6.9±1.3	7.810	0.001
Pain diagnosis					
Osteoarthritis	18 (42.9)	15 (39.5)	16 (40.0)	0.978	0.986
Low back pain	14 (33.3)	13 (34.2)	15 (37.5)		
Neuropathic pain	6 (14.3)	7 (18.4)	7 (17.5)		
Others	4 (9.5)	3 (7.9)	2 (5.0)		
Comorbidities					
Hypertension	16 (38.1)	15 (39.5)	17 (42.5)	0.172	0.918
Diabetes	8 (19.0)	7 (18.4)	9 (22.5)	0.239	0.887
Depression	6 (14.3)	7 (18.4)	8 (20.0)	0.496	0.780

Note: BMI: Body mass index; NRS: Numerical rating scale. Abbreviations are consistent throughout.

Table 2: Comparison of pain relief among three groups [mean ±SD, n (%)].

Index	Dual group (n=42)	Opioid group (n=38)	Triple group (n=40)	F/χ^2	P
Pain relief	21 (50.0)[a]	24 (63.2)	31 (77.5)	6.673	0.036
NRS reduction	2.5±1.3	3.1±1.5	4.2±1.7	12.263	<0.001
Pain relief duration (weeks)	8.5±3.2	10.2±3.8	12.6±4.1	12.070	<0.001

Note: [a] denotes a significant difference in pain relief outcomes between the Dual and Triple groups (χ^2=6.678, P=0.010); no significant differences were observed between the Opioid and Triple groups (χ^2=1.928, P=0.165) or between the Opioid and Dual groups (χ^2=1.404, P=0.236). Post hoc comparisons using Tukey HSD revealed that the Triple group had significantly greater NRS reduction than both the Dual group (mean difference 1.7, 95% CI: 0.9–2.5, P<0.001) and the Opioid group (mean difference 1.1, 95% CI: 0.3–1.9, P=0.006), while no significant difference was found between Dual and Opioid groups (P=0.180).

RESULTS

Baseline characteristics

Table 1 shows that the three groups had balanced, comparable baseline characteristics (P>0.05) but significant differences in pain intensity. The Triple group's baseline NRS score was significantly higher than the Dual and Opioid groups (P=0.001), indicating clinicians had tended to use multimodal triple therapy for patients with more severe, complex pain. Retrospectively, main pain causes were osteoarthritis (41.7%), low back pain (35.0%) and neuropathic pain (16.7%), evenly distributed among groups (P=0.986). Common complications were hypertension (40.0%) and diabetes (20.0%), with no inter-group differences (P>0.05).

Comparison of pain relief

At 6 weeks post-treatment, the Triple group showed significantly greater NRS score (Table 2) reduction and longer pain relief duration than the Opioid and Dual groups (P<0.05). The pain relief rates were 50.0% (21/42) for the Dual group, 63.2% (24/38) for the Opioid group and 77.5% (31/40) for the Triple group, with overall statistical differences (P<0.05); the Triple group was 27.5 percentage points higher than the Dual group. Pairwise comparisons revealed a significant difference between the Triple and Dual groups (P=0.010), while no statistical differences were found between the Opioid and Dual groups (P=0.236) or the Triple and Opioid groups (P=0.165), suggesting that the Triple regimen was associated with better outcomes compared with the pure non-opioid regimen.

Comparison of treatment plan adjustments

Intergroup differences in treatment adjustment rates were significant (P=0.020, Table 3), with the Dual group highest (45.2%,19/42), the Opioid group 26.3% (10/38) and the Triple group lowest (17.5%,7/40; 27.7pp absolute, 61.3% relative reduction vs Dual). Retrospective data showed Dual group adjustments centered on regimen upgrade, Opioid group adjustments were dispersed and Triple group had minimal adjustments. This may reflect that dual therapy was associated with insufficient analgesia, while triple therapy appeared to provide adequate initial intensity.

Comparison of duration of combination therapy

The triple group had the longest combined analgesic therapy duration (12.5±3.1 weeks, Table 4), significantly longer than the Dual (8.9±2.4 weeks, P<0.001) and Opioid groups (10.5±2.9 weeks, P=0.002), with a significant difference also noted between the Dual and Opioid groups (P=0.012).

Table 3: Comparison of treatment modification among three groups [n (%)].

	Dual group (n=42)	Opioid group (n=38)	Triple group (n=40)	χ^2	P
Treatment modification	19 (45.2)	10 (26.3)	7 (17.5)	7.866	0.020
Dose escalation	8 (19.0)	4 (10.5)	3 (7.5)		
Drug substitution	4 (9.5)	3 (7.9)	2 (5.0)		
Regimen upgrade	7 (16.7)	2 (5.3)	1 (2.5)		
Regimen downgrade	0 (0)	1 (2.6)	1 (2.5)		

Table 4: Duration of combination therapy and pain outcomes [mean ±SD].

Index	Dual group (n=42)	Opioid group (n=38)	Triple group (n=40)	F	P
Combination duration (weeks)	8.9±2.4	10.5±2.9	12.5±3.1	16.910	<0.001
Final NRS score	3.2±0.6	3.1±0.7	2.8±0.7	5.277	0.006

Table 5: Comparison of ARs [n (%)].

Index	Dual group (n=42)	Opioid group (n=38)	Triple group (n=40)	χ^2	P
Any adverse event	10 (23.8)	16 (42.1)	22 (55.0)	6.382	0.041
Gastrointestinal	4 (9.5)	8 (21.0)	13 (32.5)		
Nausea	2 (4.8)	3 (7.9)	5 (12.5)		
Dyspepsia	3 (7.1)	2 (5.3)	4 (10.0)		
Constipation	0 (0)	1 (2.6)	1 (2.5)		
Central nervous system	3 (7.1)	5 (13.2)	6 (15.0)		
Dizziness	2 (4.8)	3 (7.9)	4 (10.0)		
Somnolence	1 (2.4)	2 (5.3)	2 (5.0)		
Others	3 (7.1)	3 (7.9)	3 (7.5)		
Serious ARs	0 (0)	0 (0)	0 (0)		

Note: ARs: Adverse reactions.

The final NRS scores were 2.8±0.7 (Triple), 3.1±0.7 (Opioid) and 3.2±0.6 (Dual) points (F=5.277, P=0.006). However, this finding should be interpreted with caution as a longer duration may also reflect greater baseline pain severity or treatment dependency rather than treatment success alone.

Comparison of adverse drug reactions

The incidence of drug-related adverse reactions reported by Triple group patients was significantly higher (Table 5) than that of Dual group and Opioid group (P<0.05), mainly manifested as gastrointestinal reactions (nausea, indigestion) and central nervous system reactions (dizziness, drowsiness). No serious adverse events occurred in any of the three groups. However, due to the retrospective design, it is not possible to reliably grade severity or perform causality assessment for each event. For patients reporting multiple event types, it was not possible to determine whether these occurred simultaneously or sequentially.

Regression analysis

Multiple linear regression analysis of pain relief

Multiple linear regression analysis was performed with pain relief degree (NRS score reduction) as the dependent variable and treatment regimen (Table 6), baseline pain duration, baseline NRS score and other factors as independent variables. Retrospective analysis revealed that after adjusting for confounding factors, triple therapy (B=0.455, 95% CI: 0.260–0.649, P<0.001) and baseline NRS score (B=0.607, 95% CI: 0.491–0.723, P<0.001) were independent positive factors for pain relief, indicating a higher initial pain intensity correlated with a greater absolute pain reduction. The model exhibited good overall fit and independent residuals (Adjusted R^2=0.658, F=20.948, P<0.001, DW=2.074); no obvious multicollinearity was observed with all independent variables having VIF<2.

Binary logistic regression analysis of scheme adjustment

Variables with P<0.1 from univariate analysis (treatment regimen, baseline pain duration) were included in the binary logistic regression model, with treatment regimen adjustment (adjustment=1) as the dependent variable. Retrospective results showed (Tables 7 and 8) that after controlling for confounding factors, triple therapy and baseline pain duration were independent protective factors for regimen adjustment. Compared with dual non-opioid therapy, triple therapy reduced the odds of adjustment by 74.4% (OR=0.256, 95% CI: 0.090–0.729, P=0.011); each 1-week increase in baseline pain duration reduced the adjusted odds of adjustment by 8.3% (OR=0.917, 95% CI: 0.860–0.978, P=0.009).

Table 6: Multiple linear regression analysis of pain relief.

Variables	B	SE	t	P	95% CI for B		VIF
					Lower limits	Upper limits	
Constant	-2.996	1.058	-2.831	0.006	-5.094	-0.898	-
Triple therapy (Ref: Dual)	0.455	0.098	4.621	<0.001	0.260	0.649	1.178
Age	0.005	0.015	0.324	0.746	-0.025	0.035	1.085
Female (Ref: Male)	-0.057	0.156	-0.367	0.715	-0.367	0.253	1.071
BMI	0.034	0.020	1.727	0.087	-0.005	0.074	1.059
Pain duration	0.009	0.011	0.812	0.419	-0.013	0.030	1.056
Baseline NRS	0.607	0.058	10.381	<0.001	0.491	0.723	1.241
Osteoarthritis (Ref: Others)	0.081	0.084	0.963	0.338	-0.085	0.247	1.083
Hypertension	0.199	0.157	1.269	0.207	-0.112	0.510	1.054
Diabetes	-0.060	0.190	-0.313	0.755	-0.437	0.317	1.032
Depression	-0.163	0.203	-0.806	0.422	-0.565	0.238	1.059

Adjusted R^2=0.658, F=20.948, P<0.001, DW=2.074.

Table 7: Univariate analysis.

Variable	Treatment modification (n=36)	No modification (n=84)	OR (95% CI)	P
Age (years)	57.0±5.2	57.5±5.0	0.981 (0.913–1.054)	0.591
Female	21 (58.3)	47 (56.0)	1.102 (0.507–2.395)	0.806
BMI (kg/m²)	25.6±3.8	26.0±4.1	0.972 (0.881–1.072)	0.571
Pain duration (months)	16.9±5.6	21.0±7.8	0.917 (0.860–0.978)	0.009
Baseline NRS	6.2±1.4	6.4±1.4	0.912 (0.700–1.187)	0.493
Treatment regimen				
Dual	19 (52.8)	23 (27.4)	1	
Opioid	10 (27.8)	28 (33.3)	0.432 (0.171–1.092)	0.076
Triple	7 (19.4)	33 (39.3)	0.257 (0.094–0.701)	0.008
Pain diagnosis				
Osteoarthritis	13 (36.1)	37 (44.0)	1	
Low back pain	14 (38.9)	28 (33.3)	1.423 (0.590–3.433)	0.433
Neuropathic pain	6 (16.7)	14 (16.7)	1.220 (0.404–3.682)	0.726
Others	3 (8.3)	5 (6.0)	1.708 (0.365–7.994)	0.493
Hypertension	12 (33.3)	36 (42.9)	0.667 (0.297–1.497)	0.326
Diabetes	7 (19.4)	17 (20.2)	0.952 (0.359–2.527)	0.921
Depression	5 (13.9)	16 (19.0)	0.688 (0.232–2.035)	0.500

Table 8: Binary logistic regression analysis.

Variables	B	SE	Wald	P	OR	95% CI for OR	
						Lower limits	Upper limits
Opioid therapy (Ref: Dual)	-0.709	0.501	2.007	0.157	0.492	0.184	1.313
Triple therapy (Ref: Dual)	-1.363	0.534	6.513	0.011	0.256	0.090	0.729
Pain duration	-0.086	0.033	6.902	0.009	0.917	0.860	0.978
Constant	1.395	0.680	4.207	0.040	4.035	-	-

Note: H-L test χ^2=12.617, P=0.126, Nagelkerke R^2=0.172.

Sensitivity analysis using ANCOVA

To adjust for baseline pain severity, a one-way ANCOVA was performed with 6-week NRS as the dependent variable, baseline NRS as a covariate and treatment group as a fixed factor. The assumption of homogeneity of regression slopes was met [Group × Baseline NRS interaction, F(2,114)=0.87, P=0.42, not shown]. After adjusting for baseline NRS, there was a statistically significant main effect of treatment group on 6-week NRS [F(2,116)=13.64, P<0.001, partial η^2=0.190]. Bonferroni-corrected pairwise comparisons (Table 9) showed that the Triple group had significantly lower adjusted 6-week NRS than both the Dual group (adjusted mean difference = −0.94, 95% CI: −1.41 to −0.48, P<0.001) and the Opioid group (adjusted mean difference = −0.76, 95% CI: −1.21 to −0.30, P<0.001). No significant difference was observed between the Dual and Opioid groups (P=0.954). This sensitivity analysis supports the primary finding that triple therapy was associated with better pain outcomes, independent of baseline pain severity, but it remains an association and does not imply causation.

Table 9: Adjusted 6-week NRS by treatment group.

Group	Adjusted mean (SE)	95% CI	Pairwise comparison vs. Triple
Dual (n=42)	3.44 (0.13)	3.18-3.69	Mean diff = -0.94, P<0.001
Opioid (n=38)	3.26 (0.13)	2.99-3.52	Mean diff = -0.76, P<0.001
Triple (n=40)	2.50 (0.13)	2.23-2.76	Reference

DISCUSSION

The concept of multimodal analgesia originates from the understanding of the complexity of pain transmission pathways. The generation and transmission of pain signals involve multiple processes such as peripheral receptor activation, spinal dorsal horn signal integration, ascending conduction pathways and cortical processing. Different types of analgesic drugs act on different targets and combined application can achieve complementary mechanisms and synergistic effects (Katz *et al*., 2011). The core of combination therapy lies in the complementary mechanisms and synergistic effects, which have been validated in the management of various chronic diseases. Similarly, multimodal combined analgesia for chronic pain achieves the goal of optimizing analgesic efficacy by simultaneously acting on peripheral sensitization, central conduction and neuropathic mechanisms. In this study, the Triple group used a triple combination of NSAIDs, weak opioid drugs and adjuvant analgesics, targeting peripheral inflammation, central sensitization and neuropathic pain components, respectively, thus demonstrating the favorable pain relief outcomes. This result is consistent with the conclusion of previous RCTs that multimodal combination therapy is superior to single drug or simple dual therapy in controlling moderate to severe chronic pain (Ong *et al*., 2010). Although the Triple group had the highest pain-relief rate, the incidence of adverse reactions increased accordingly. This trade-off reflects the benefit-to-risk ratio of combination therapy. The adverse reactions of the Triple group are mainly concentrated in gastrointestinal reactions and central nervous system symptoms, which is consistent with the known adverse reaction spectrum of NSAIDs and opioid drugs. However, no serious adverse events occurred in any of the three groups in this study, indicating that the safety of the multimodal triple therapy is acceptable under standardized monitoring and reasonable dosage. Among the CNCP patients included in this study, the comorbidity rate of depression was 14.3% - 20.0%, indicating that attention should be paid to the HPA axis functional status and its impact on treatment efficacy when formulating analgesic plans. In clinical practice, patients' gastrointestinal and cardiovascular risk factors should be fully evaluated and if necessary, proton pump inhibitors should be combined to protect the gastric mucosa. Adverse reaction monitoring and patient education should also be strengthened (Lanza *et al*., 2009). The adjustment rate of the treatment plan in the Dual group was as high as 45.2%, significantly higher than the other two groups and mainly manifested as plan upgrade (upgrading from a dual non opioid plan to an opioid containing plan). This phenomenon reveals the problem of insufficient steps in real clinical practice: some patients with moderate to severe pain initially adopt non opioid dual therapy, but need to frequently adjust the regimen due to unsatisfactory analgesic effects. According to the World Health Organization analgesic ladder principle, for patients with moderate pain, direct use of second or third tier treatment can be considered to avoid treatment delays and patient dissatisfaction caused by repeated adjustments (Vargas-Schaffer, 2010; Wiffen *et al*., 2017; Busse *et al*., 2018).

The multiple linear regression analysis in this study showed that, after controlling for confounding factors, triple therapy (B=0.455, P<0.001) and baseline NRS score (B=0.607, P<0.001) were independent predictors of pain relief. The significant advantages of triple therapy validate the core concept of multimodal analgesia. In this study, triple therapy was associated with an additional decrease of 0.45 points (95% CI: 0.260–0.649) in NRS score, which is clinically significant in chronic pain management and may translate into comprehensive improvements in functional status, sleep quality and mental health. However, the duration of pain did not have a significant impact in this study (B=0.009, P=0.419), indicating that the degree of disease chronicity does not reduce the efficacy of triple therapy, which provides a basis for active treatment of patients with long-term illness. The baseline NRS score, as the strongest predictor (β=0.607), reflects the statistical phenomenon of regression to the mean and the cumulative effect of clinical practice. On the one hand, statistically speaking, high baseline scores provide greater room for decline; on the other hand, patients with severe pain in clinical practice may have stronger treatment motivation and compliance, while physicians pay more attention to them and adjust their treatment more actively (Letzen *et al*., 2019). However, this discovery should not be misinterpreted as the heavier the pain, the easier it is to relieve. Age, gender, BMI, pain causes, and complications (hypertension, diabetes, depression) did not show a significant impact, suggesting that the efficacy of triple therapy has cross-population stability and is not significantly interfered with by the traditional efficacy modification factors. This broad-spectrum efficacy feature enhances the clinical value of the results, especially in scenarios where primary healthcare resources are limited and fine pain classification cannot be performed. The

triple therapy can be used as an empirical treatment option (Gilron *et al*., 2013). However, the lack of a significant association between depression and B (B=-0.163, P=0.422) may be due to sample size limitations or the absence of standardized depression scales in this study. In the future, it is necessary to increase the sample size and include psychological assessments to further explore the topic.

The binary logistic regression of this study showed that the triple regimen (NSAIDs+ opioids+ Adjuvant drugs) was an independent protective factor for treatment adjustment, reducing adjustment risk by 74.4% compared to the dual non opioid regimen (OR=0.256, 95% CI: 0.090–0.729), while the weak opioid+ Adjuvant drug regimen showed a protective trend (OR=0.492) but did not reach statistical significance, suggesting that early and sufficient combination of NSAIDs is the key to reducing treatment instability. For each 1-week increase in baseline pain duration, the adjusted risk decreased by 8.3% (OR=0.917), indicating that patients with longer disease courses tend to have stable pain phenotypes or have undergone multiple protocol screenings. In this study, triple therapy was an independent protective factor for adjusting treatment plans, which may be due to its multi-target synergistic effect that can more effectively control moderate to severe or mixed pain, thereby reducing subsequent protocol upgrades caused by insufficient analgesia. In traditional stepwise analgesia, insufficient initial treatment intensity often leads to subsequent adjustments; Early standardized multimodal combination, by simultaneously intervening in peripheral, central and neurological mechanisms, can achieve more stable and sufficient pain relief, reducing the need for adjustment (Finnerup *et al*., 2016, Gilron *et al*., 2013). Although the explanatory power of Nagelkerke R^2=0.172 in the binary logistic regression model of this study is low, it is universal in real-world studies of chronic pain (Varrassi *et al*., 2017). The adjustment of chronic pain treatment is influenced by multiple factors such as the patient's psychological state, physician prescription habits and social support and cannot be fully predicted by clinical indicators alone (Cohen *et al*., 2021). However, the classification approach (escalating patients to the final regimen, with escalation counted as an adjustment) may have introduced time-dependent bias, artificially strengthening the observed association between initial dual therapy and higher adjustment rates. Therefore, these findings should be interpreted with caution. Although the proportion of unexplained variations in the model is relatively high, the core predictive factors (OR=0.256 for triple therapy and OR=0.917 for pain duration) have clear effect sizes and clinical interventions and still have important practical guidance value. Future research could incorporate psychological and social factors such as pain self-efficacy and treatment expectations, or use machine learning algorithms to handle non-linear relationships to improve prediction accuracy (Obermeyer and Emanuel, 2016). The longer therapy duration in the Triple group (12.5±3.1 weeks) should not be automatically interpreted as favorable persistence. Alternative explanations include higher baseline pain severity, potential opioid dependence, or slower symptom resolution in complex pain phenotypes. Thus, this finding may reflect disease chronicity and treatment dependency rather than treatment success alone. The Triple group had significantly higher baseline NRS (6.9 vs. 5.8/6.2, P=0.001), reflecting treatment-selection bias (more severe pain received intensified therapy). Although adjusted in regression, this bias cannot be fully eliminated due to potential nonlinearity, regression to the mean and unmeasured confounders. Thus, the observed superior pain relief in the Triple group should not be interpreted as causal. The Triple group had significantly higher baseline NRS (P=0.001), reflecting preferential prescription of intensified therapy to more severe pain. Although adjusted in regression, residual confounding cannot be ruled out. Therefore, the observed superior pain relief should be viewed as an association, not causal and requires confirmation in randomized trials.

The findings of this study have important implications for individualized treatment strategies for CNCP. Firstly, pain assessment should be the core basis for treatment decisions and baseline pain duration should be included as a consideration factor in the selection of combination therapy regimens. Secondly, for patients with moderate to severe pain, early adoption of standardized multimodal triple therapy may reduce frequent adjustments to subsequent treatment plans, improve treatment satisfaction and compliance. Thirdly, during combination therapy, it is necessary to strengthen monitoring for adverse reactions, especially in the early stages of medication initiation and dosage adjustment. Timely identification and treatment of adverse reactions can help improve treatment tolerance (Moore *et al*., 2015b). From a health economics perspective, frequent adjustments to treatment plans may increase medical resource consumption and the burden on patients. The 45.2% protocol adjustment rate in the Dual group of this study means that nearly half of the patients require additional outpatient visits, medication changes and dose titration procedures. Early adoption of more effective multimodal solutions may have higher initial costs, but if the number of subsequent adjustments can be reduced and long-term pain control can be improved, it may have better returns (Gustorff *et al*., 2008). Future research can further evaluate the long-term economic impacts of different combination therapy strategies. The results of this study are consistent with the recommendations of EFIC, the Neuropathic Pain Special Interest Group and the Canadian CNCP guidelines (Finnerup *et al*., 2016; Busse *et al*., 2017), which suggests that multimodal combination therapy should be considered for moderate to severe pain. This study provides real-world evidence to support this.

Study limitations

This study has the following limitations: (1) the retrospective study design may have selection bias and information bias and the integrity of some clinical data depends on the quality of medical records; (2) Single center research with limited sample size requires further verification of the extrapolation of results; (3) The follow-up time is relatively short and the cumulative effects of long-term pain control, drug tolerance and adverse reactions require longer observation; (4) Not included in the comprehensive assessment of pain on quality of life, functional status and mental health, these dimensions have important value in evaluating the overall effectiveness of combined analgesic treatment; (5) Failed to obtain medication compliance data for all patients and differences in compliance may affect the accuracy of efficacy evaluation; (6) The combination use of non-pharmacological therapies (such as physical therapy and cognitive-behavioral therapy) is not included, while multimodal analgesia should include the integration of pharmacological and non-pharmacological therapies. Future prospective studies with multiple centers, large samples and long follow-up periods are needed to further validate the conclusions of this study.

(7) Non-randomized design with confounding by indication. Regimens were assigned clinically, resulting in differences in baseline pain severity across groups. Multivariable adjustment cannot eliminate residual confounding, so reported associations are not causal. (8) Heterogeneity within treatment groups. Pooling different adjuvants (e.g., gabapentinoids, SNRIs, TCAs) and various weak opioids without subgroup analysis may obscure drug-specific effects, limiting interpretability and reproducibility. Future larger studies should perform subgroup analyses. (9) Ambiguity of treatment duration interpretation. A longer therapy duration in the Triple group may reflect either favorable persistence or greater disease severity/treatment dependence, so this endpoint should be interpreted with caution. (10) Unmeasured confounders. Despite multivariable adjustment, unmeasured factors (adherence, dose intensity, psychological factors, non-pharmacological therapies and pain subtype severity) likely remain, so observed associations should not be interpreted as causal. (11) Time-dependent and attribution bias. Analyzing escalated patients on the final regimen while counting escalation as an adjustment may bias the observed associations; future studies should use initial-regimen grouping or time-varying models.

CONCLUSION

In summary, this retrospective study systematically elucidated differences in analgesic combination therapy patterns among CNCP patients in real-world clinical settings and their associations with pain intensity and treatment regimen adjustments. The main conclusions include: (1) The multimodal triple therapy (NSAIDs+ opioids+ adjuvant drugs) was associated with the highest pain relief rate; (2) Although the dual non opioid regimen has good safety, the adjustment rate of the treatment plan was relatively high for patients with moderate to severe pain when using this regimen; (3) Triple therapy and baseline pain duration were independently associated with a lower likelihood of treatment plan adjustment; (4) Triple therapy and baseline NRS score were independently associated with the degree of pain relief.

This study provides important real-world evidence to optimize the individualized multimodal analgesia strategy for CNCP, supporting stratification of combination therapy based on pain phenotype. Early adoption of standardized multimodal regimens for moderate to severe pain patients may help reduce frequent adjustments to subsequent treatment plans.

Acknowledgment

None.

Author's contributions

Linlin Chao: Developed and planned the study, performed experiments, interpreted results, edited and refined the manuscript with a focus on critical intellectual contributions; Weixing Li: Participated in collecting, assessing and interpreting the data, made significant contributions to data interpretation and manuscript preparation; Jinsen Zhang, Zhenyu Cai: Provided substantial intellectual input during the drafting and revision of the manuscript.

Funding

There was no funding.

Data availability statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethical approval

This study was approved by the First Affiliated Hospital of Xiamen University Ethics Committee (approval No. 2026-083, dated April 22, 2026). Written informed consent was obtained from all participants before enrollment. This study was performed in adherence with the RECORD guidelines. See supplementary file for the RECORD checklist.

Conflict of interest

The authors declare no conflict of interest.

Supplementary data

https://www.pjps.pk/uploads/2026/08/SUP1785835707.pdf

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