

Cannabinoid-Opioid Combination Therapy for Chronic and Cancer Pain¹Gurpreet Singh Popli, Professor, Department of Anesthesia, CK Birla Hospital, Punjabi Bagh, New Delhi, India²Sanjeev, Department of Anesthesia, CK Birla Hospital, Punjabi Bagh, New Delhi, India³Lalit Sehrawat, Department of Anesthesia, CK Birla Hospital, Punjabi Bagh, New Delhi, India⁴Mandeep Malhotra, Department of Oncology, CK Birla Hospital, Punjabi Bagh, New Delhi, India**Corresponding Author:** Gurpreet Singh Popli, Professor, Department of Anesthesia, CK Birla Hospital, Punjabi Bagh, New Delhi, India**How to citation this article:** Gurpreet Singh Popli, Sanjeev, Lalit Sehrawat, Mandeep Malhotra, “Cannabinoid-Opioid Combination Therapy for Chronic and Cancer Pain”, IJMACR– October– 2026, Volume – 9, Issue – 5, P. No. 224 – 230.**Open Access Article:** © 2026 Gurpreet Singh Popli, et al. This is an open access journal and article distributed under the terms of the creative common’s attribution license (<http://creativecommons.org/licenses/by/4.0>). Which allows others to remix, tweak, and build upon the work non - commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.**Type of Publication:** Original Research Article**Conflicts of Interest:** Nil**Abstract****Background:** Chronic and cancer-related pain are major global health burdens. Opioids remain the mainstay of moderate-to-severe pain management, but long-term use is limited by tolerance, dependence, and adverse effects, prompting interest in opioid-sparing adjuncts such as cannabinoids.**Objective:** To compare pain reduction, opioid consumption, and adverse-effect profiles between opioid monotherapy and combined opioid–cannabinoid therapy in patients with chronic non-cancer or cancer-related pain.**Methods:** This retrospective observational chart review included 46 adult patients treated at CK Birla Hospital (January 2023–December 2025) who received either opioid therapy alone or opioid therapy with adjunctive cannabinoids. Pain intensity (Numeric Rating Scale, NRS), opioid dose (morphine milligram equivalent,MME), and adverse events were abstracted from hospital records. Continuous variables were compared using independent- and paired-samples t-tests; categorical variables using the chi-square or Fisher's exact test; multivariate regression was used to adjust for confounders. Analyses were performed in SPSS, with significance set at $p < 0.05$.**Results:** The two groups were comparable at baseline for age (58.4 ± 11.2 vs 56.9 ± 12.5 years) and NRS pain score (7.8 ± 1.1 vs 8.0 ± 1.0). The opioid + cannabinoid group achieved significantly greater reduction in NRS pain scores than opioid monotherapy ($p = 0.002$), together with a 27.9% reduction in opioid consumption expressed as MME ($p < 0.001$). Constipation incidence was significantly lower in the adjunct group ($p = 0.018$).**Conclusion:** Adjunctive cannabinoid therapy was associated with superior analgesia, a clinically meaningful opioid-sparing effect, and improved

gastrointestinal tolerability compared with opioid monotherapy in this retrospective cohort. Prospective, adequately powered studies are warranted to confirm these findings and clarify long-term safety.

Keywords: Cannabinoids, Opioids, Chronic Pain, Cancer Pain, Opioid-Sparing Effect, Morphine Milligram Equivalent, Retrospective Study

Introduction

Chronic pain and cancer-related pain remain among the most prevalent and burdensome conditions encountered in clinical practice, with substantial effects on quality of life and functional capacity. Population-based estimates place the global prevalence of chronic pain at approximately 20%,¹ while pain affects an estimated 39–66% of patients with cancer depending on disease stage, rising further in advanced and metastatic disease.² Effective analgesia is therefore a cornerstone of both oncological and perioperative care.

Opioids have long been the mainstay of treatment for moderate-to-severe pain, particularly in oncology. The World Health Organization's analgesic ladder, introduced in 1986, continues to inform stepwise pain management strategies worldwide,³ and strong opioids such as morphine, fentanyl, and oxycodone remain widely used for nociceptive and cancer-related pain. However, long-term opioid therapy carries well-recognised limitations, including tolerance, physical dependence, opioid-induced hyperalgesia, constipation, sedation, and respiratory depression. Evidence supporting sustained benefit of opioids in chronic non-cancer pain is limited,⁴ and the risks of dependence and overdose mortality associated with prolonged use necessitate cautious, judicious prescribing.⁵ These concerns, amplified by the global opioid crisis, have

prompted growing interest in multimodal and opioid-sparing analgesic strategies.

Cannabinoids have emerged as a potential adjunct or alternative in pain management. The endocannabinoid system, acting principally through CB1 and CB2 receptors, plays a recognised role in modulating nociceptive signalling. Delta-9-tetrahydrocannabinol (THC) contributes analgesic and psychoactive effects, while cannabidiol (CBD) is associated with anti-inflammatory and anxiolytic properties. Systematic reviews indicate that cannabinoids provide modest analgesic benefit in chronic pain, particularly of neuropathic origin,⁶ and may improve sleep quality and overall well-being in patients with chronic pain.⁷ In oncology, cannabinoid formulations combining THC and CBD have shown improvement in pain scores among patients with opioid-refractory cancer pain compared with placebo, alongside ancillary benefits such as appetite stimulation, nausea control, and mood enhancement.⁷ Current evidence nonetheless supports the use of cannabinoids as adjuncts rather than as replacements for opioids in severe cancer pain.

Preclinical and clinical data suggest a synergistic interaction between the opioid and endocannabinoid systems, both of which modulate nociception through G-protein-coupled receptors and shared neurotransmitter pathways. Cannabinoid co-administration has been proposed to enhance opioid analgesia while permitting dose reduction, with a systematic review estimating an opioid-sparing effect of approximately 20–30% when cannabinoids are used adjunctively.⁸ This interaction may also mitigate opioid-related adverse effects, particularly gastrointestinal symptoms such as constipation. Comparatively, cannabinoids appear to carry a more favourable safety profile than opioids, with

no clinically significant respiratory depression reported; the principal adverse effects are dizziness, sedation, and cognitive impairment, particularly at higher THC concentrations, with a substantially lower dependence liability than opioids.

Despite this rationale, comparative clinical data on combined opioid–cannabinoid therapy versus opioid monotherapy remain limited, particularly from real-world, retrospective cohorts. The global burden of chronic pain also varies by region (Figure 1), underscoring the need for context-specific comparative evidence. We therefore conducted a retrospective observational study to compare pain reduction, opioid consumption, and adverse-effect profiles between opioid monotherapy and combined opioid–cannabinoid therapy in patients with chronic non-cancer or cancer-related pain.

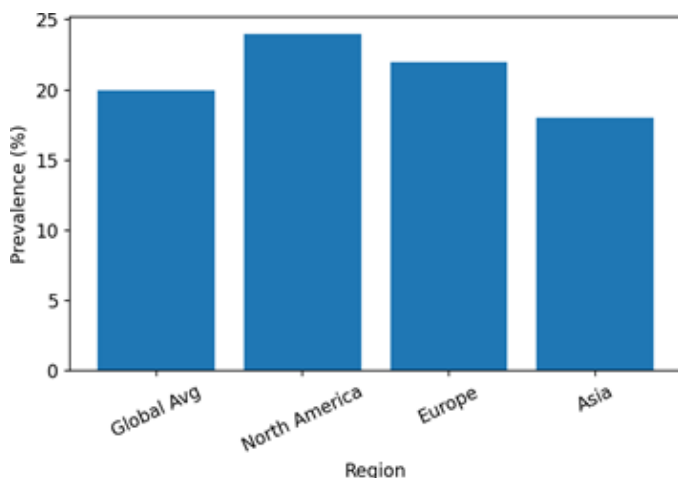


Figure 1. Estimated prevalence of chronic pain by region (global average and selected regions).¹

Objectives

Primary objective: To compare the reduction in pain scores (NRS) between opioid monotherapy and opioid + cannabinoid therapy.

Secondary objectives: (i) to assess the opioid-sparing effect, measured as reduction in morphine milligram equivalent (MME) dose; (ii) to compare

the incidence of adverse effects between groups; and (iii) to evaluate functional improvement associated with each treatment approach.

Materials and Methods

Study Design and Setting

This was a retrospective observational chart-review study conducted jointly by the Departments of Anaesthesia and Oncology at CK Birla Hospital, Punjabi Bagh, New Delhi, India. Records of eligible patients managed between January 2023 and December 2025 were reviewed.

Ethical considerations

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. As a retrospective chart review involving no direct patient intervention, a waiver of individual informed consent was requested from the institutional ethics committee. All data were anonymised prior to analysis, with no personal identifiers extracted or disclosed, and records were retained on a secure institutional database.

Participants

Inclusion criteria: age ≥ 18 years; chronic pain of more than 3 months' duration or cancer-related pain; receipt of opioid therapy; a minimum follow-up of 4 weeks; and availability of complete medical records.

Exclusion criteria: incomplete medical records; history of substance abuse; severe psychiatric illness; and concurrent participation in an experimental therapy protocol.

A total of 46 patients meeting these criteria were included. The sample size was determined pragmatically on the basis of feasibility and the effect sizes reported in prior comparative literature on opioid-sparing cannabinoid adjuncts.⁸ Patients were classified into two comparison groups according to the treatment received:

(1) opioid-only therapy, and (2) opioid therapy combined with adjunctive cannabinoid treatment.

Data collection

Data were abstracted from the hospital electronic and physical medical records by the investigating team and included: demographic characteristics; pain intensity recorded on the 11-point Numeric Rating Scale (NRS, 0–10); opioid dose expressed as morphine milligram equivalent (MME); cannabinoid use (formulation and duration); and documented adverse events, including constipation, sedation, and cognitive impairment.

Statistical analysis

Continuous variables are expressed as mean $\pm$ standard deviation (SD) and were compared between groups using the independent-samples t-test; within-group change from baseline was assessed using the paired-samples t-test. Categorical variables were analysed using the chi-square test or Fisher's exact test, as appropriate to expected cell counts. Multivariate regression analysis was used to adjust for potential confounders (including age, baseline pain severity, and pain aetiology) when comparing outcomes between groups. A two-tailed p-value <0.05 was considered statistically significant throughout. All analyses were performed using SPSS statistical software.

Results

Forty-six patients with chronic non-cancer or cancer-related pain met the inclusion criteria and were included in the analysis. The opioid-only and opioid + cannabinoid groups were closely matched at baseline for age and pain severity (Table 1), indicating that the groups were broadly comparable prior to treatment.

Table 1: Baseline characteristics of the study cohort (mean $\pm$ SD)

Variable	Opioid monotherapy	Opioid + cannabinoid
Mean age, years (mean $\pm$ SD)	58.4 $\pm$ 11.2	56.9 $\pm$ 12.5
Baseline NRS pain score (mean $\pm$ SD)	7.8 $\pm$ 1.1	8.0 $\pm$ 1.0

Figure 2 illustrates the distribution of pain aetiology within the overall cohort, which was predominantly musculoskeletal (40%) and neuropathic (25%) in origin, with cancer-related pain accounting for 20% of cases and mixed presentations for 15%.

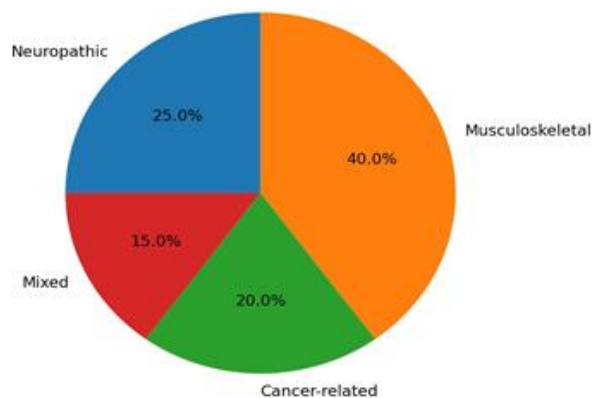


Figure 2. Distribution of chronic pain types within the study cohort.

Primary outcome: pain reduction

Patients receiving combined opioid–cannabinoid therapy demonstrated a significantly greater reduction in NRS pain scores from baseline compared with those receiving opioid monotherapy ($p = 0.002$), consistent with a clinically meaningful analgesic benefit of adjunctive cannabinoid treatment.

Secondary outcomes: opioid-sparing effect and adverse events

Patients in the adjunct group achieved a 27.9% reduction in opioid dose (MME) relative to baseline, a

significantly greater opioid-sparing effect than that observed with opioid monotherapy ($p < 0.001$) (Figure 3). This magnitude of dose reduction is consistent with opioid-sparing effects of 20–30% previously reported for adjunctive cannabinoid therapy.⁸

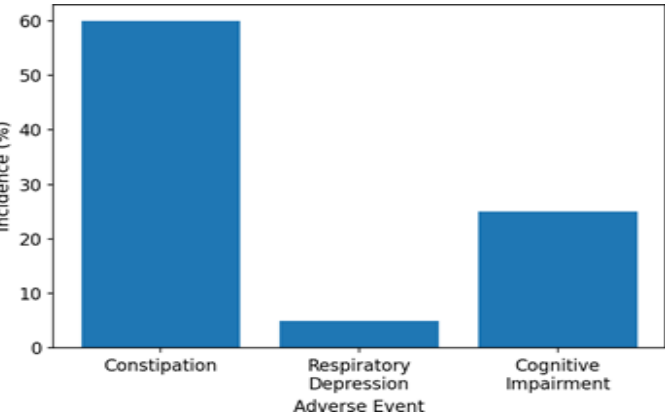


Figure 3. Relative opioid dose reduction associated with adjunctive cannabinoid therapy.

Adverse-effect analysis showed that constipation — the most frequently documented opioid-related adverse effect in the overall cohort (Figure 4) — occurred significantly less often in the opioid + cannabinoid group than in the opioid-only group ($p = 0.018$), consistent with the hypothesised opioid-sparing reduction in gastrointestinal adverse effects. Respiratory depression was uncommon across the cohort, and cognitive impairment was reported at intermediate frequency (Figure 4).

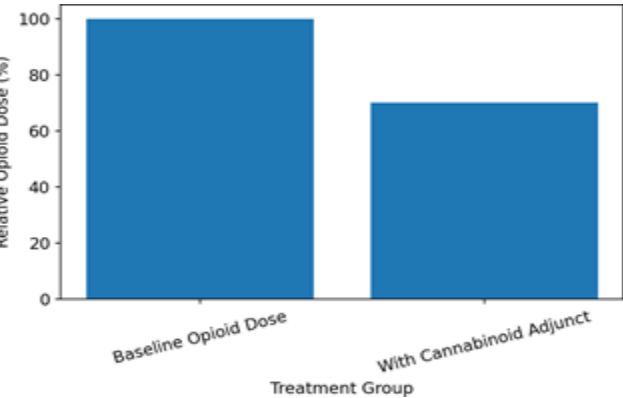


Figure 4: Incidence of opioid-related adverse events in the overall cohort.

Table 2: Summary of primary and secondary outcome comparisons

Outcome	Finding	p-value
Reduction in NRS pain score, opioid + cannabinoid vs opioid monotherapy	Significantly greater with combination therapy	0.002
Reduction in opioid consumption (MME), adjunct vs monotherapy	27.9% reduction	<0.001
Incidence of constipation	Significantly reduced in adjunct group	0.018

Discussion

In this retrospective cohort of 46 patients with chronic non-cancer or cancer-related pain, adjunctive cannabinoid therapy combined with opioids was associated with significantly greater pain reduction, a clinically relevant 27.9% opioid-sparing effect, and a significantly lower incidence of constipation compared with opioid monotherapy. These findings are consistent with the broader literature suggesting a synergistic interaction between the endocannabinoid and opioid systems, in which cannabinoid co-administration enhances analgesia while permitting meaningful opioid dose reduction.^{7,8} The observed opioid-sparing effect in this cohort falls within the 20–30% range previously reported in systematic reviews of adjunctive cannabinoid use,⁸ lending external consistency to our findings despite the modest sample size.

The reduction in constipation incidence observed with adjunctive cannabinoid therapy is plausibly explained by the accompanying reduction in opioid dose, since

opioid-induced constipation is dose-dependent. This observation aligns with the more favourable overall safety profile historically attributed to cannabinoids relative to opioids, particularly the absence of clinically significant respiratory depression, which remains a leading cause of opioid-related mortality.⁵ Nonetheless, cannabinoids are not without risk: dizziness, sedation, and cognitive impairment are recognised adverse effects, particularly at higher THC concentrations, and their potential for dependence — while lower than that of opioids — is not negligible.

These results should be interpreted in light of important limitations inherent to the study design. First, the retrospective, single-centre design is susceptible to selection and information bias, and unmeasured confounders (such as differences in underlying disease severity, concomitant medication use, or psychosocial factors) cannot be fully excluded despite multivariate adjustment. Second, the overall sample size of 46 patients is modest, limiting statistical power for subgroup analyses and the precision of effect-size estimates. Third, cannabinoid formulation, dosing, and duration of use were not standardised across patients, which may affect the generalisability of the opioid-sparing effect observed. Fourth, the absence of long-term follow-up precludes conclusions regarding durability of analgesic benefit or delayed adverse effects. Finally, as an observational study, causal inference regarding the opioid–cannabinoid interaction cannot be firmly established.

Despite these limitations, the findings support the existing rationale for considering cannabinoids as an adjunct — rather than a replacement — for opioid therapy in appropriately selected patients with chronic or

cancer-related pain, particularly where opioid-sparing is clinically desirable.

Prospective, randomised, and adequately powered studies are needed to confirm the magnitude of the analgesic and opioid-sparing benefits observed here, to standardise cannabinoid dosing regimens, and to characterise long-term safety and dependence risk in this population.

Conclusion

In this retrospective observational study, adjunctive cannabinoid therapy combined with opioids was associated with significantly greater pain relief, a clinically meaningful opioid-sparing effect of approximately 28%, and reduced incidence of opioid-related constipation compared with opioid monotherapy in patients with chronic non-cancer or cancer-related pain. These findings support cannabinoids as a promising adjunctive strategy for opioid-sparing multimodal analgesia, warranting confirmation in prospective controlled trials.

Declarations

Ethics approval and consent to participate: The study was conducted in accordance with the Declaration of Helsinki. A waiver of informed consent was requested given the retrospective, non-interventional design; all data were anonymised.

Consent for publication: Not applicable (no identifiable patient data are presented).

Availability of data and materials: The datasets analysed during the current study are available from the corresponding author on reasonable request.

Author contributions: G.S.P. conceived and designed the study and supervised its conduct; Sanjeev and L.S. contributed to data acquisition and analysis; M.M. contributed oncology case data and critical revision of

the manuscript. All authors reviewed and approved the final manuscript.

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