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Ten-Year Outcomes of Medical Cannabis for Chronic Low Back Pain: Opioid Reduction, Pain Relief, and Functional Improvement in 1,000 Patients

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Abstract

Purpose

To evaluate 10-year outcomes of medical cannabis therapy on opioid use, pain intensity, functional disability, concomitant medication use, and adverse events in cannabis-naïve chronic low back pain (CLBP) patients, with particular attention to clinically meaningful outcomes defined by established minimal clinically important difference (MCID) thresholds.

Methods

Single-center longitudinal observational study of 1,000 consecutive cannabis-naïve CLBP patients from a registry database (2015–2024), reported following STROBE guidelines. Primary outcome: morphine milligram equivalents (MMEQ). Secondary outcomes: Numeric Rating Scale (NRS) for pain intensity, Oswestry Disability Index (ODI) for functional disability, cannabis dosing patterns, adverse events, and concomitant medication use. Pre-specified MCID thresholds: ≥50% MMEQ reduction, ≥ 30% NRS reduction, ≥ 10-point ODI improvement. Statistical analyses included paired t-tests for completers and linear mixed-effects models for sensitivity analyses.

Results

Of 1,000 enrolled patients, 638 (63.8%) completed 10-year follow-up. Among completers, MMEQ decreased from 62.8 ± 35.7 to 6.4 ± 7.1 mg/day (− 89.8%, $p < 0.001$); NRS from 8.71 ± 1.23 to 1.37 ± 1.71 (− 84.2%, $p < 0.001$); ODI from 52.9 ± 11.9% to 36.8 ± 14.9% (16.1-point reduction, − 30.4%, $p < 0.001$). MCID responders: 91.2% for MMEQ, 96.6% for NRS, 62.1% for ODI. Substantial polypharmacy reductions occurred: tramadol/tapentadol − 84.0 percentage points (pp), benzodiazepines − 73.5 pp, SSRIs − 71.9 pp, gabapentinoids − 30.7 pp. True tolerability adverse events occurred in 11.4% of visits; serious psychiatric events in 0.02%.

Conclusions

In this uncontrolled observational study, medical cannabis therapy was associated with reductions in opioid use, pain intensity, and functional disability over 10 years, accompanied by polypharmacy reduction and acceptable tolerability. Effect sizes substantially exceeded RCT benchmarks (e.g., − 0.6 NRS difference vs. placebo in a recent phase 3 trial), suggesting observational biases contribute to these findings. These hypothesis-generating data warrant validation in randomized controlled trials.

Introduction

Chronic low back pain (CLBP) represents a major global health burden and the leading cause of disability worldwide. The Global Burden of Disease Study 2021 reported that low back pain affected 619 million people globally in 2020, with projections exceeding 843 million prevalent cases by 2050 [1]. Low back pain consistently ranks as the foremost cause of years lived with disability (YLDs), contributing to both individual suffering and societal economic costs estimated at $560–635 billion annually in the United States alone [2, 3]. The condition is multifactorial, with biological, psychological, and social determinants influencing its development and persistence [4].

The natural history of CLBP presents significant clinical challenges. While acute low back pain episodes often resolve spontaneously, approximately one-third of patients experience improvement within one year, while the majority demonstrate persistent symptoms requiring ongoing management [5, 6]. The biopsychosocial model of CLBP, articulated by Waddell, emphasizes the interplay between biological, psychological, and social factors in the development and maintenance of pain [7]. Psychological factors such as anxiety, depression, fear avoidance, and catastrophizing significantly affect pain perception and disability outcomes, complicating management [8, 9].

Current clinical guidelines recommend a stepped-care approach beginning with non-pharmacological interventions. The American College of Physicians guidelines and WHO recommendations endorse exercise therapy, cognitive behavioral therapy (CBT), multidisciplinary rehabilitation, and mindfulness-based stress reduction as first-line treatments [10, 11]. However, when conservative measures fail, pharmacological options are limited. Nonsteroidal anti-inflammatory drugs (NSAIDs) provide modest relief but carry gastrointestinal and cardiovascular risks with long-term use [12]. Gabapentinoids and antidepressants show inconsistent efficacy, with effect sizes typically below the MCID threshold [13].

The opioid crisis has created urgent need for safer analgesic alternatives. Prescription opioid use for chronic pain management has contributed to over 100,000 overdose deaths annually in the United States, with CLBP patients representing a substantial proportion of long-term opioid users [14, 15]. Current guidelines recommend against routine opioid prescriptions for chronic non-cancer pain due to risks of tolerance, dependence, and adverse events, yet evidence-based alternatives remain critically needed [16, 17].

Medical cannabis has emerged as a potential opioid-sparing agent through its interaction with the endocannabinoid system (ECS). The ECS is a complex lipid signaling network essential for maintaining physiological homeostasis and regulating pain perception, inflammation, appetite, and mood [18]. This system comprises three main components: cannabinoid receptors (primarily CB1 and CB2), endogenous ligands (endocannabinoids), and metabolic enzymes [19]. CB1 receptors are predominantly located in the central nervous system, particularly in the spinal cord dorsal horn, basal ganglia, cerebellum, and hippocampus. Their activation by cannabinoids inhibits release of excitatory neurotransmitters such as glutamate and substance P, thereby reducing pain signal transmission [20]. CB2 receptors are primarily expressed on immune cells and modulate inflammatory responses by regulating cytokine release [21].

Signal transduction involves inhibition of adenylyl cyclase, decreased cAMP formation, and activation of mitogen-activated protein kinases (MAPK) [22].

The two principal endocannabinoids, anandamide (AEA) and 2-arachidonoylglycerol (2-AG), are synthesized on demand and act as retrograde messengers to modulate synaptic transmission [23]. Phytocannabinoids, particularly Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD), activate these receptors to modulate nociception, inflammation, and central sensitization. THC functions as a partial agonist at CB1 and CB2 receptors, while CBD has lower receptor affinity but modulates endocannabinoid tone and interacts with serotonergic and vanilloid receptors [24, 25].

Preclinical studies provide robust evidence for opioid-sparing effects of cannabinoids. Meta-analysis of animal studies demonstrated that the median effective dose (ED50) of morphine administered with THC is approximately 3.5 times lower than morphine alone [26, 27]. Clinical evidence, however, remains more limited. A systematic review by Noori et al. found very low certainty evidence that observational studies suggested adding cannabis reduced opioid use by 22.5 morphine milligram equivalents (MME), while randomized controlled trials in cancer pain patients showed little or no effect [28]. Notably, most existing studies have short follow-up periods (< 2 years), limited sample sizes, and heterogeneous patient populations. Recent systematic reviews suggest cannabinoids may be similarly effective to opioids for chronic non-cancer pain while causing fewer treatment discontinuations due to adverse events [29]. Emerging evidence specific to CLBP supports these findings: a prospective clinical trial of 249 patients with chronic low back pain demonstrated significant dose-dependent acute pain relief with THC-containing edibles ($r = 0.14$, $p<.05$), with pain reductions sustained over a 2-week ad libitum use period across all cannabinoid formulations and minimal adverse events [47]. The mechanistic basis for opioid-sparing effects involves substantial crosstalk between cannabinoid and opioid receptor systems at anatomical, neurochemical, and behavioral levels [44]. CB1 and mu-opioid receptors are densely co-localized in central nervous system regions mediating pain and withdrawal, particularly the locus coeruleus and periaqueductal gray [44, 45]. Importantly, human laboratory studies demonstrate that THC's analgesic effects are pharmacologically distinct from its psychoactive properties; in chronic pain patients on opioids, total pain relief scores showed no correlation with measures of subjective "high" on the Addiction Research Center Inventory, suggesting these effects operate through separable mechanisms [46].

Critical gaps remain in the existing literature. A 2020 systematic review specifically examining cannabis for low back pain identified only six studies meeting inclusion criteria from 124 screened and found no randomized controlled trials specifically addressing cannabis for CLBP, concluding there was a significant lack of quality evidence and calling for well-designed clinical trials [48]. This evidence gap was partially addressed by a landmark 2025 phase 3 randomized controlled trial (n = 820) demonstrating that a full-spectrum cannabis extract achieved statistically significant pain reduction versus placebo in CLBP patients (mean difference − 0.6 NRS points; 54.1% vs. 39.5% achieved ≥ 30% pain reduction; NNTB = 6.8) with benefits sustained through 12 months [49]. However, no study has reported 10-year outcomes of medical cannabis therapy specifically in CLBP patients, and few have systematically evaluated

polypharmacy reduction beyond opioids. This study evaluates 10-year outcomes of medical cannabis therapy in 1,000 consecutive cannabis-naïve CLBP patients, examining effects on opioid consumption, pain intensity, functional disability, adverse events, and concomitant medication use. We hypothesized that medical cannabis therapy would be associated with sustained, clinically meaningful improvements defined by established MCID thresholds.

Methods

Study design and setting

This was a single-arm longitudinal observational study reported following Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [30]. Data were extracted from a prospective registry database maintained at a specialized orthopedic pain clinic. The registry was established in 2015 to systematically track outcomes of patients receiving medical cannabis for chronic musculoskeletal pain conditions. This study was approved by the institutional ethics committee, and all patients provided written informed consent for registry participation and data use.

Study population

We included 1,000 consecutive cannabis-naïve patients with CLBP enrolled between January 2015 and December 2015. Inclusion criteria were: (1) CLBP diagnosis confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) demonstrating structural abnormalities including spinal stenosis, disc degeneration, vertebrogenic low back pain, or spondylolisthesis; (2) continuous opioid use for ≥ 1 year prior to enrollment; (3) cannabis-naïve status defined as no lifetime cannabis use, verified by patient history and urine drug screening; (4) age ≥ 18 years; and (5) failure of or inadequate response to conventional treatments including physical therapy, NSAIDs, and opioid therapy. Exclusion criteria included incomplete baseline MMEQ documentation, active malignancy, pregnancy, severe psychiatric disorders requiring hospitalization, substance use disorder other than prescription opioids, and prior cannabis exposure.

Intervention

Patients received medical cannabis under physician supervision according to national regulatory guidelines. Cannabis products were obtained from licensed producers and included dried flower for vaporization (avoiding combustion to reduce respiratory risks) and cannabis oils for oral/sublingual administration. Initial dosing followed a "start low, go slow" approach: THC-dominant products typically began at 2.5–5 mg THC, with titration over 2–4 weeks based on response and tolerability. Patients were educated on administration techniques, potential adverse effects, and driving restrictions. Concurrent medications including opioids were permitted to continue or taper at the discretion of treating physicians based on clinical response; no standardized tapering protocol was mandated.

Follow-up and retention

Patients were assessed at baseline and annually for 10 years (2015–2024). Data collection was performed by dedicated clinical research staff independent of treating physicians to minimize assessment bias. Of 1,000 enrolled patients, 638 (63.8%) completed all 10 annual assessments. Attrition occurred as follows: 72 patients (7.2%) were lost during Years 1–2 (42 patient preference, 18 relocation, 12 lost to follow-up), 10 patients (1.1%) during Years 2–3 (6 unrelated deaths, 4 lost to follow-up), and 280 patients (30.5%) during Years 3–10 (approximately 5% annually, primarily due to patient preference, relocation, or loss to follow-up). No patients discontinued due to lack of efficacy or intolerable adverse events after Year 2.

Outcome measures

The primary outcome was opioid consumption measured in morphine milligram equivalents (MMEQ) per day, calculated using standard equianalgesic conversion factors [31]. Secondary outcomes included: (1) pain intensity assessed using the 11-point Numeric Rating Scale (NRS, 0–10, with 0 indicating no pain and 10 worst imaginable pain) [32]; (2) functional disability assessed using the Oswestry Disability Index (ODI, 0–100%, with higher scores indicating greater disability), a validated instrument widely used in spine research [33]; (3) cannabis dosing including total monthly consumption (g/month) and THC/CBD content; (4) adverse events categorized as tolerability-related (true drug effects) or efficacy-related (insufficient pain relief); and (5) concomitant medication use including tramadol/tapentadol, benzodiazepines, selective serotonin reuptake inhibitors (SSRIs), and gabapentinoids.

Minimal clinically important difference thresholds

MCID thresholds were pre-specified based on established literature. For opioid reduction, we used ≥ 50% MMEQ reduction as the threshold for clinically meaningful opioid sparing. For pain intensity, we used ≥ 30% NRS reduction, which represents the widely accepted threshold for meaningful pain improvement in chronic pain populations and corresponds to a "much better" improvement on patient global impression scales [34, 35]. For functional disability, we used ≥ 10-point absolute improvement in ODI, the established MCID for low back pain patients [36, 37]. Individual responder rates were calculated as the proportion of patients achieving each MCID threshold.

Statistical analysis

Primary analyses used paired t-tests comparing baseline to Year 10 outcomes among the 638 completers. Effect sizes were calculated using Cohen's d. Sensitivity analyses employed two approaches: (1) linear mixed-effects models with random intercepts for patients, treating time as a continuous variable and including all 8,089 observations across all timepoints (lme4 package in R version 4.5); these models assumed data were missing at random (MAR) and provided annualized effect estimates with 95% confidence intervals; and (2) last observation carried forward (LOCF) imputation for

the full cohort. We report means with standard deviations, 95% confidence intervals, and effect sizes where appropriate. Statistical significance was set at $p < 0.05$ (two-tailed). All analyses were conducted in R version 4.5.

Results

Baseline characteristics

Baseline characteristics of the 1,000 enrolled patients are presented in Table 1. Mean age was 48.9 ± 15.7 years (range 22–78), 64.0% were male, and mean BMI was 27.2 ± 4.3 kg/m². Pain duration averaged 9.8 ± 6.3 years, indicating a population with established chronicity. Structural diagnoses confirmed by imaging included spinal stenosis (48.6%), disc degeneration (26.9%), and vertebrogenic low back pain (22.9%); 42% of patients had multiple pathologies. Baseline pain and disability scores indicated a severely affected population consistent with tertiary referral: MMEQ 59.6 ± 36.4 mg/day (range 10–185), NRS 8.64 ± 1.20, and ODI 52.7 ± 11.7% (moderate-to-severe disability). At baseline, polypharmacy was common: 89.7% used tramadol/tapentadol, 78.8% benzodiazepines, 77.7% SSRIs, and 31.3% gabapentinoids. Completers (n = 638) did not differ significantly from non-completers (n = 362) in baseline demographics, pain severity, or medication use (all $p > 0.05$).

Table 1
Baseline Characteristics (N = 1,000)

Characteristic	Value
Age, years (mean ± SD)	48.9 ± 15.7
Male, n (%)	640 (64.0%)
BMI, kg/m² (mean ± SD)	27.2 ± 4.3
Pain duration, years (mean ± SD)	9.8 ± 6.3
Structural diagnosis, n (%)	
Spinal stenosis (M48.06)	486 (48.6%)
Disc degeneration (M51.16)	269 (26.9%)
Vertebrogenic LBP (M54.5x)	229 (22.9%)
Other	16 (1.6%)
Full cohort baseline (N = 1,000)	
MMEQ, mg/day	59.6 ± 36.4
NRS (0–10)	8.64 ± 1.20
ODI (%)	52.7 ± 11.7
Completers baseline (n = 638)	
MMEQ, mg/day	62.8 ± 35.7
NRS (0–10)	8.71 ± 1.23
ODI (%)	52.9 ± 11.9
Completers baseline medications, n (%)	
Tramadol/Tapentadol	572 (89.7%)
Benzodiazepines	503 (78.8%)
SSRIs	495 (77.7%)
Gabapentinoids	200 (31.3%)

BMI=body mass index; LBP = low back pain; MMEQ=morphine milligram equivalents; NRS=Numeric Rating Scale; ODI=Oswestry Disability Index; SSRIs=selective serotonin reuptake inhibitors

Retention and follow-up

Overall retention at Year 10 was 63.8% (638/1000). Annual retention rates were: Year 1: 100%, Year 2: 92.8%, Year 3: 91.8%, Year 5: 82.5%, Year 7: 74.5%, Year 10: 63.8%. A total of 8,089 patient-visits were included in mixed-effects analyses (mean 8.1 visits per patient). Reasons for dropout were: patient

preference (42.0%, including relocation to areas without cannabis access), geographic relocation (18.2%), loss to follow-up (33.3%), and death unrelated to study (6.5%, all from cardiovascular or other non-pain causes). Importantly, no dropouts were attributed to intolerable adverse events, treatment failure, or development of cannabis use disorder.

Primary outcome: opioid consumption

Among the 638 completers, MMEQ decreased substantially from baseline 62.8 ± 35.7 mg/day to Year 10: 6.4 ± 7.1 mg/day, representing an 89.8% reduction (absolute reduction: 56.4 mg/day; 95% CI: 53.8–59.0; $p < 0.001$; Cohen's $d = 2.19$, indicating a very large effect). This reduction substantially exceeds the 22.5 MME reduction reported in meta-analyses of observational studies [28]. Opioid reduction was rapid in the first year (MMEQ 3.1 ± 8.0 at Year 1, 94.8% reduction from baseline) and remained stable through Year 10. At Year 10, 91.2% (582/638) of completers achieved the pre-specified MCID of ≥ 50% MMEQ reduction, and 6.6% (42/638) achieved complete opioid cessation (MMEQ = 0).

Secondary outcomes: pain intensity

Pain intensity decreased from baseline NRS 8.71 ± 1.23 to Year 10: 1.37 ± 1.71 (− 84.2% reduction; absolute reduction: 7.34 points; 95% CI: 7.18–7.50; $p < 0.001$; Cohen's $d = 4.92$). This magnitude of pain reduction substantially exceeds that reported in systematic reviews of cannabinoids for chronic pain, which typically show reductions of 0.5–1.0 points on a 10-point scale [38, 39]. At Year 10, 96.6% (616/638) achieved the pre-specified MCID of ≥ 30% NRS reduction, and 89.2% (569/638) achieved NRS ≤ 3 (mild pain or less). The pain reduction exceeded the MCID threshold by more than three-fold.

Secondary outcomes: functional disability

Functional disability improved more gradually than pain outcomes. ODI decreased from baseline 52.9 ± 11.9% to Year 10: 36.8 ± 14.9% (− 30.4% relative reduction; absolute reduction: 16.1 points; 95% CI: 14.6–17.6; $p < 0.001$; Cohen's $d = 1.19$). This exceeds the established 10-point MCID for ODI [36, 37]. At Year 10, 62.1% (396/638) achieved ≥ 10-point ODI improvement. Notably, ODI improvement was temporally delayed relative to pain and opioid outcomes, with minimal change through Year 5 (50.5 ± 13.9%) but substantial improvement between Years 7 (47.2 ± 14.5%) and 10 (36.8 ± 14.9%). This pattern suggests that functional restoration may require sustained pain relief and gradual reconditioning over years.

Sensitivity analyses

Mixed-effects models including all 8,089 observations confirmed sustained improvements and provided annualized effect estimates. MMEQ decreased by 5.3 mg/day per year (95% CI: −5.6 to − 5.0, $p < 0.001$), NRS decreased by 0.73 points per year (95% CI: −0.76 to − 0.70, $p < 0.001$), and ODI decreased by 1.6 points per year (95% CI: −1.8 to − 1.4, $p < 0.001$). LOCF imputation for all 1,000 patients yielded similar endpoint estimates: MMEQ 6.8 ± 7.4, NRS 1.52 ± 1.82, ODI 38.4 ± 15.2. The consistency across analytical approaches supports robustness of findings despite attrition.

Cannabis dosing

Cannabis consumption among completers followed an initial titration pattern then stabilized. Mean consumption reached 38.7 ± 14.2 g/month by Year 2 and remained relatively constant through Year 10 (47.5 ± 15.3 g/month; mean across Years 1–10: 40.9 ± 14.8 g/month; Fig. 3). Mean THC content was 7.8 g/month and CBD content 2.0 g/month, yielding an approximate THC:CBD ratio of 3.8:1. Administration routes included vaporized dried flower (62%), oral oils (31%), and combined routes (7%). No significant dose escalation was observed over the 10-year period, arguing against tolerance development.

Concomitant medication reduction

Substantial polypharmacy reductions occurred among completers (Table 2). Tramadol/tapentadol use decreased from 89.7% to 5.6% (− 84.0 percentage points), benzodiazepines from 78.8% to 5.3% (− 73.5 pp), SSRIs from 77.7% to 5.8% (− 71.9 pp), and gabapentinoids from 31.3% to 0.6% (− 30.7 pp). These reductions were clinically driven rather than protocol-mandated, reflecting individual physician-patient decisions based on symptom response. The pattern of polypharmacy reduction paralleled opioid reduction, occurring primarily in the first 2 years.

Table 2
Concomitant Medication Use (n = 638 Completers)

Medication	Baseline	Year 10	Change (pp)
Tramadol/Tapentadol	89.7%	5.6%	−84.0
Benzodiazepines	78.8%	5.3%	−73.5
SSRIs	77.7%	5.8%	−71.9
Gabapentinoids	31.3%	0.6%	−30.7

pp=percentage points. Reductions were clinically driven, not protocol-mandated. SSRIs=selective serotonin reuptake inhibitors

Adverse events

Across 8,089 patient-visits, adverse events were reported at 2,142 visits (26.5%). However, after distinguishing true tolerability events from efficacy-related complaints (insufficient pain relief), the tolerability adverse event rate was 11.4% (925 visits; Fig. 5). Most common tolerability events were: dry mouth (5.2%), gastrointestinal symptoms including nausea and appetite changes (3.6%), red eyes/conjunctival irritation (1.6%), hypotension (0.4%), cognitive symptoms (0.3%), palpitations (0.2%), and dizziness (0.1%). These rates compare favorably to published meta-analyses reporting dizziness in up to 25% of patients and treatment discontinuation rates of 8–13% with cannabinoids [38]. Serious psychiatric adverse events (psychosis/major mood disorder) occurred at 2 visits (0.02%). No hospitalizations, deaths, treatment discontinuations due to adverse events, or cases of cannabis use disorder were recorded.

Discussion

This 10-year observational study represents the longest follow-up of medical cannabis therapy specifically in CLBP patients and demonstrates sustained, clinically meaningful improvements exceeding pre-specified MCID thresholds for opioid reduction, pain relief, and functional disability. The magnitude and durability of these findings merit careful consideration in the context of existing evidence and current treatment paradigms for chronic low back pain.

The 89.8% reduction in opioid consumption substantially exceeds prior reports. Noori et al.'s meta-analysis of observational studies found a weighted mean reduction of 22.5 MME, while our completers demonstrated a mean reduction of 56.4 MME [28]. Several factors may explain this difference. First, our population was cannabis-naïve, potentially yielding greater response than cannabis-experienced patients included in other studies. Second, the 10-year duration allowed for gradual opioid tapering that shorter studies cannot capture. Third, our patients had confirmed structural pathology and high baseline opioid doses (59.6 MME), representing a population with substantial room for improvement. Fourth, physician-supervised titration and licensed products may optimize outcomes compared to self-directed use. The clinical significance of these reductions is underscored by the 91.2% MCID responder rate. The mechanistic basis for these opioid-sparing effects likely involves the well-characterized crosstalk between cannabinoid and opioid receptor systems [44]. CB1 and mu-opioid receptors share G-protein coupled signaling pathways and are densely co-localized in pain-modulating brain regions including the periaqueductal gray and locus coeruleus [44, 45]. A randomized controlled trial demonstrated that dronabinol (synthetic THC) at 20–30 mg reduced objective opioid withdrawal symptoms by up to 48% compared to placebo in opioid-dependent individuals, supporting functional interactions between these receptor systems [45]. Importantly, Issa et al. demonstrated in a crossover trial that THC’s analgesic effects in chronic pain patients on opioids were independent of its psychoactive properties; measures of subjective “high” showed no correlation with pain relief scores [46]. This separation suggests that cannabinoid analgesia may be achievable without proportional increases in abuse liability—a finding consistent with our observation that sustained pain relief occurred without evidence of dose escalation or cannabis use disorder.

The polypharmacy reductions warrant particular attention. The 71–84 percentage point decreases in tramadol/tapentadol, benzodiazepines, and SSRIs suggest that medical cannabis may address multiple symptom domains simultaneously. Chronic pain patients frequently require polypharmacy to manage pain, sleep disturbance, anxiety, and depression, each of which carries risks of adverse effects and drug interactions [40]. The endocannabinoid system's role in modulating pain, mood, anxiety, and sleep through CB1 and CB2 receptor activation in diverse brain regions may explain this broad effect profile [18, 19]. CB1 receptors in limbic structures modulate anxiety and emotional responses, while effects on sleep-wake regulation involve hypothalamic endocannabinoid signaling [41]. These findings have important implications for medication burden, drug interaction risk, and healthcare costs in CLBP populations.

The pain reduction observed in our cohort (NRS 8.71 to 1.37, − 84.2%) substantially exceeds effects reported in randomized controlled trials. The recent Karst et al. phase 3 RCT (n = 820) of a full-spectrum

cannabis extract for CLBP demonstrated a mean difference of only − 0.6 NRS points versus placebo at 12 weeks (absolute reduction − 1.9 points), with 54.1% achieving ≥ 30% pain reduction compared to 39.5% with placebo [49]. Our observational findings (96.6% responders) exceed these RCT benchmarks by a substantial margin. Similarly, systematic reviews of conventional CLBP treatments report mean NRS reductions of 0.5–1.0 points for NSAIDs, 0.5–1.5 points for opioids, and 0.5–1.0 points for gabapentinoids [10, 13], and meta-analyses of cannabinoids for chronic pain report effect sizes of only 0.5–1.0 points [38, 39]. The marked discrepancy between our observational findings and RCT evidence warrants careful interpretation. The magnitude of improvement in our cohort likely reflects multiple factors beyond pharmacological effect, including regression to the mean, placebo and expectancy effects, changes in co-interventions, and survivorship bias toward treatment responders due to attrition—issues inherent to uncontrolled observational designs. The 36% attrition over 10 years may have enriched our completer cohort with “super-responders,” inflating apparent effect sizes. Nevertheless, several observations provide some reassurance: the stability of pain reduction over 10 years (exceeding typical placebo effect duration), the correlation between cannabis dosing and outcomes in mixed-effects models, and consistency across sensitivity analyses including LOCF imputation.

The functional disability improvement (ODI 52.9% to 36.8%, 16.1-point reduction) exceeded the established 10-point MCID [36, 37]. However, only 62.1% of completers achieved this threshold, compared to > 90% for pain and opioid outcomes. This discrepancy likely reflects the multifactorial nature of disability in CLBP, which involves not only nociception but also deconditioning, psychological factors (fear avoidance, catastrophizing, depression), structural limitations, and social circumstances [4, 7, 8]. Notably, ODI improvement was temporally delayed relative to pain outcomes, with the most substantial improvement occurring after Year 7. This suggests that functional restoration may require sustained pain relief, gradual reconditioning, and psychological adaptation that develop over years—a finding with important implications for treatment expectations and study design in CLBP interventions. Long-term follow-up studies of multidisciplinary pain programs have similarly shown that functional improvements may continue to develop over 1–3 years [42].

The tolerability profile was favorable, with true adverse events at 11.4% of visits, predominantly mild and consistent with known cannabinoid effects. The 0.02% rate of serious psychiatric events (2/8,089 visits) compares favorably to psychiatric adverse event rates reported with high-potency cannabis products in other populations. Published meta-analyses report dizziness in up to 25% of patients, somnolence in 8%, and treatment discontinuation rates of 4–13% with cannabinoids [38]. A prospective CLBP trial of 249 patients similarly reported no serious adverse events with edible cannabis products over 2 weeks of ad libitum use, with only 15 tachycardia events (non-significantly distributed across THC, CBD, and combined product groups) [47]. The dramatic increase in THC potency in recreational cannabis products (from 4–5% in the 1990s to 15–20% currently) has raised concerns about psychosis risk, with daily high-potency use associated with nearly five-fold increased risk of psychotic disorders [43]. Our lower adverse event rates may reflect physician supervision, use of licensed products with known cannabinoid content, gradual titration protocols, and exclusion of patients with severe psychiatric disorders.

Limitations

Several limitations warrant acknowledgment and careful consideration when interpreting these findings. First and most critically, the single-arm observational design precludes causal inference and provides very low certainty evidence compared to randomized controlled trials. Without a control group, we cannot adequately distinguish treatment effects from regression to the mean, placebo effects, natural history, changes in co-interventions, or selection bias toward patients more likely to improve. The magnitude of our observed effects substantially exceeds those reported in the recent Karst et al. phase 3 RCT of cannabis for CLBP (− 0.6 NRS points vs. placebo) [49], underscoring that our findings should be interpreted as hypothesis-generating rather than definitive evidence of treatment efficacy. The attrition rate (36.2% over 10 years), while comparable to other long-term pain studies, likely introduces survivorship bias; completers may represent “super-responders” who experienced favorable outcomes, potentially inflating apparent effect sizes. Sensitivity analyses using mixed-effects models (which assume missing at random) and LOCF imputation yielded similar results, but these methods cannot fully address the potential for informative dropout. With 36.2% attrition primarily attributed to non-efficacy reasons, the completer cohort may over-represent sustained responders, as commonly observed in long-term pain registries.

Second, the single-center design limits generalizability to other populations, healthcare systems, and cannabis products. Our patients were selected from a specialized orthopedic pain clinic (tertiary referral), and findings may not extend to primary care populations, other healthcare systems with different cannabis regulations, or patients with non-specific low back pain. Third, opioid and other medication tapering was clinically driven rather than protocolized, introducing potential confounding by indication. Fourth, we did not assess healthcare utilization, quality of life (e.g., SF-12/SF-36), work productivity, or psychological outcomes (depression, anxiety, fear avoidance), limiting understanding of broader treatment impact. Fifth, we could not assess for cannabis use disorder using validated instruments, although no clinical cases were identified.

Clinical implications and future directions

These observational findings should be interpreted as hypothesis-generating rather than practice-changing. While the sustained associations observed over 10 years and the polypharmacy reductions are intriguing, the marked discrepancy between our effect sizes and those reported in the recent Karst et al. phase 3 RCT [49] underscores the limitations of uncontrolled observational data. The RCT demonstrated that rigorous placebo-controlled evaluation yields much more modest effect sizes (NNTB = 6.8 for ≥ 30% pain reduction), consistent with the broader cannabinoid literature showing low-certainty evidence of modest benefit [50, 51]. Our findings may reflect a combination of true pharmacological effect, the natural history of CLBP in a motivated treatment-seeking population, expectancy effects, and survivorship bias. Given this very low certainty evidence, these findings require validation before routine clinical adoption. Future pragmatic randomized trials should: (1) compare cannabis to active controls; (2) include diverse CLBP populations including primary care patients; (3) employ standardized cannabis

formulations; (4) assess long-term outcomes including functional measures and quality of life; (5) evaluate psychological mediators; and (6) systematically monitor for cannabis use disorder using validated instruments.

Conclusions

In this 10-year single-arm observational study, medical cannabis therapy was associated with reductions in opioid use (− 89.8%), pain intensity (− 84.2%), and functional disability (− 30.4%), with high proportions of patients achieving pre-specified MCID thresholds. Substantial polypharmacy reductions and acceptable tolerability were observed. However, these effect sizes substantially exceed those reported in recent placebo-controlled RCTs of cannabis for CLBP, suggesting that observational biases including survivorship bias, regression to the mean, and placebo effects likely contribute to the magnitude of observed associations. These hypothesis-generating findings provide the longest follow-up data for medical cannabis in CLBP and warrant cautious interpretation pending validation in adequately powered randomized controlled trials.

Declarations

Author Contribution

MK and DR contributed equally to this work. MK: Data curation, formal analysis, writing – original draft. DR: Conceptualization, methodology, data curation, formal analysis, writing – original draft, writing – review & editing, supervision. EL: Supervision, Writing – review & editing. FQ: Data curation, investigation. WAR: Data curation, investigation. HM: Data curation, investigation. MY: Supervision, Writing-review & editing. All authors approved the final manuscript.

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Data Availability

All data supporting the findings of this study are available within the paper and its Supplementary Information additionally The datasets analyzed during the current study are available from the corresponding author on reasonable request.

References

1. GBD 2021 Low Back Pain Collaborators (2023) Global, regional, and national burden of low back pain, 1990–2020, its attributable risk factors, and projections to 2050. Lancet Rheumatol 5:e316–

e329
2. Hoy D, March L, Brooks P et al (2014) The global burden of low back pain: estimates from the Global Burden of Disease 2010 study. Ann Rheum Dis 73:968–974
3. Dahlhamer J, Lucas J, Zelaya C et al (2018) Prevalence of chronic pain and high-impact chronic pain among adults—United States, 2016. MMWR Morb Mortal Wkly Rep 67:1001–1006
4. Hartvigsen J, Hancock MJ, Kongsted A et al (2018) What low back pain is and why we need to pay attention. Lancet 391:2356–2367
5. Pengel LH, Herbert RD, Maher CG, Refshauge KM (2003) Acute low back pain: systematic review of its prognosis. BMJ 327:323
6. da Silva T, Mills K, Brown BT et al (2017) Risk of recurrence of low back pain: a systematic review. J Orthop Sports Phys Ther 47:305–313
7. Waddell G (1987) A new clinical model for the treatment of low-back pain. Spine 12:632–644
8. Pincus T, Burton AK, Vogel S, Field AP (2002) A systematic review of psychological factors as predictors of chronicity/disability in prospective cohorts of low back pain. Spine 27:E109–E120
9. Vlaeyen JWS, Linton SJ (2000) Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. Pain 85:317–332
10. Qaseem A, Wilt TJ, McLean RM et al (2017) Noninvasive treatments for acute, subacute, and chronic low back pain. Ann Intern Med 166:514–530
11. World Health Organization (2023) WHO guideline for non-surgical management of chronic primary low back pain in adults in primary and community care settings. WHO, Geneva
12. Enthoven WTM, Roelofs PDDM, Deyo RA et al (2016) Non-steroidal anti-inflammatory drugs for chronic low back pain. Cochrane Database Syst Rev 2:CD012087
13. Enke O, New HA, New CH et al (2018) Anticonvulsants in the treatment of low back pain and lumbar radicular pain: a systematic review and meta-analysis. CMAJ 190:E786–E793
14. CDC (2023) Drug Overdose Deaths, 2002–2022. NCHS Data Brief 491:1–8
15. Volkow ND, McLellan AT (2016) Opioid abuse in chronic pain—misconceptions and mitigation strategies. N Engl J Med 374:1253–1263
16. Dowell D, Haegerich TM, Chou R (2016) CDC guideline for prescribing opioids for chronic pain—United States, 2016. JAMA 315:1624–1645
17. Chou R, Turner JA, Devine EB et al (2015) The effectiveness and risks of long-term opioid therapy for chronic pain. Ann Intern Med 162:276–286
18. Lu HC, Mackie K (2021) Review of the endocannabinoid system. Biol Psychiatry Cogn Neurosci Neuroimaging 6:607–615
19. Guindon J, Hohmann AG (2009) The endocannabinoid system and pain. CNS Neurol Disord Drug Targets 8:403–421
20. Howlett AC, Barth F, Bonner TI et al (2002) International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. Pharmacol Rev 54:161–202

21. Turcotte C, Blanchet MR, Laviolette M, Bhomley MA (2016) The CB2 receptor and its role as a regulator of inflammation. Cell Mol Life Sci 73:4449–4470
22. Ibsen MS, Connor M, Glass M (2017) Cannabinoid CB1 and CB2 receptor signaling and bias. Cannabis Cannabinoid Res 2:48–60
23. Blankman JL, Cravatt BF (2013) Chemical probes of endocannabinoid metabolism. Pharmacol Rev 65:849–871
24. Pertwee RG (2008) The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids. Br J Pharmacol 153:199–215
25. Vuckovic S, Srebro D, Vujovic KS et al (2018) Cannabinoids and pain: new insights from old molecules. Front Pharmacol 9:1259
26. Nielsen S, Sabioni P, Trigo JM et al (2017) Opioid-sparing effect of cannabinoids: a systematic review and meta-analysis. Neuropsychopharmacology 42:1752–1765
27. Nielsen S, Picco L, Murnion B et al (2022) Opioid-sparing effect of cannabinoids for analgesia: an updated systematic review and meta-analysis. Neuropsychopharmacology 47:1315–1330
28. Noori A, Busse JW, Engles A et al (2021) Opioid-sparing effects of medical cannabis or cannabinoids for chronic pain: a systematic review and meta-analysis. BMJ Open 11:e047717
29. Jeddi HM, Busse JW, Sadeghirad B et al (2024) Cannabis for medical use versus opioids for chronic non-cancer pain: a systematic review and network meta-analysis. BMJ Open 14:e068182
30. von Elm E, Altman DG, Egger M et al (2007) The STROBE statement: guidelines for reporting observational studies. Lancet 370:1453–1457
31. Nielsen S, Degenhardt L, Hoban B, Gisev N (2016) A synthesis of oral morphine equivalents (OME) for opioid utilisation studies. Pharmacoepidemiol Drug Saf 25:733–737
32. Hjermstad MJ, Fayers PM, Haugen DF et al (2011) Studies comparing Numerical Rating Scales, Verbal Rating Scales, and Visual Analogue Scales for assessment of pain intensity. J Pain Symptom Manage 41:1073–1093
33. Fairbank JC, Pynsent PB (2000) The Oswestry Disability Index. Spine 25:2940–2952
34. Dworkin RH, Turk DC, Wyrwich KW et al (2008) Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain 9:105–121
35. Salaffi F, Stancati A, Silvestri CA et al (2004) Minimal clinically important changes in chronic musculoskeletal pain intensity measured on a numerical rating scale. Eur J Pain 8:283–291
36. Ostelo RW, de Vet HC (2005) Clinically important outcomes in low back pain. Best Pract Res Clin Rheumatol 19:593–607
37. Lauridsen HH, Hartvigsen J, Manniche C et al (2006) Responsiveness and minimal clinically important difference for pain and disability instruments in low back pain patients. BMC Musculoskelet Disord 7:82
38. Whiting PF, Wolff RF, Deshpande S et al (2015) Cannabinoids for medical use: a systematic review and meta-analysis. JAMA 313:2456–2473

39. Aviram J, Samuelly-Leichtag G (2017) Efficacy of cannabis-based medicines for pain management: a systematic review and meta-analysis. Pain Physician 20:E755–E796
40. Manchikanti L, Kaye AM, Knezevic NN et al (2017) Responsible, safe, and effective prescription of opioids for chronic non-cancer pain. Pain Physician 20:S3–S92
41. Murillo-Rodriguez E, Pandi-Perumal SR, Monti JM (2021) Cannabinoids and Sleep. Springer, Cham
42. Eklund A, Jensen I, Lohela-Karlsson M et al (2019) Long-term outcomes in multidisciplinary treatment of chronic low back pain: costs, comorbidities and healthcare. J Rehabil Med 51:450–460
43. Di Forti M, Quattrone D, Freeman TP et al (2019) The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe. Lancet Psychiatry 6:427–436
44. De Aquino JP, Bahji A, Gómez O, Sofuoglu M (2022) Alleviation of opioid withdrawal by cannabis and delta-9-tetrahydrocannabinol: a systematic review of observational and experimental human studies. Drug Alcohol Depend 241:109702
45. Lofwall MR, Babalonis S, Nuzzo PA, Elayi SC, Walsh SL (2016) Opioid withdrawal suppression efficacy of oral dronabinol in opioid dependent humans. Drug Alcohol Depend 164:143–150
46. Issa MA, Narang S, Jamison RN et al (2014) The subjective psychoactive effects of oral dronabinol studied in a randomized, controlled crossover clinical trial for pain. Clin J Pain 30:472–478
47. Melendez SN, Ortiz Torres M, Lisano JK et al (2024) Edible cannabis for chronic low back pain: associations with pain, mood, and intoxication. Front Pharmacol 15:1464005
48. First L, Schutte N, Douglas JA (2020) Cannabis use and low-back pain: a systematic review. Cannabis Cannabinoid Res 5:283–289
49. Karst M, Wippermann S, Ahrens J et al (2025) Full-spectrum extract from Cannabis sativa DKJ127 for chronic low back pain: a phase 3 randomized placebo-controlled trial. Nat Med 31:2910–2919
50. Henson JD, Vitetta L, Hall S (2022) Tetrahydrocannabinol and cannabidiol medicines for chronic pain and mental health conditions. Inflammopharmacology 30:1167–1178
51. Bhaskar A, Bell A, Boivin M et al (2021) Consensus recommendations on dosing and administration of medical cannabis to treat chronic pain: results of a modified Delphi process. J Cannabis Res 3:22

Tables

Table 1. Baseline characteristics of the study population (N=1,000). Values are mean±SD or n (%). BMI=body mass index; LBP=low back pain; MMEQ=morphine milligram equivalents; NRS=Numeric Rating Scale; ODI=Oswestry Disability Index; SSRIs=selective serotonin reuptake inhibitors.

Table 1. Baseline Characteristics (N=1,000)

Characteristic	Value
Age, years (mean±SD)	48.9±15.7
Male, n (%)	640 (64.0%)
BMI, kg/m² (mean±SD)	27.2±4.3
Pain duration, years (mean±SD)	9.8±6.3
Structural diagnosis, n (%)	
Spinal stenosis (M48.06)	486 (48.6%)
Disc degeneration (M51.16)	269 (26.9%)
Vertebrogenic LBP (M54.5x)	229 (22.9%)
Other	16 (1.6%)
Full cohort baseline (N=1,000)	
MMEQ, mg/day	59.6±36.4
NRS (0–10)	8.64±1.20
ODI (%)	52.7±11.7
Completers baseline (n=638)	
MMEQ, mg/day	62.8±35.7
NRS (0–10)	8.71±1.23
ODI (%)	52.9±11.9
Completers baseline medications, n (%)	
Tramadol/Tapentadol	572 (89.7%)
Benzodiazepines	503 (78.8%)
SSRIs	495 (77.7%)
Gabapentinoids	200 (31.3%)

BMI=body mass index; LBP=low back pain; MMEQ=morphine milligram equivalents; NRS=Numeric Rating Scale; ODI=Oswestry Disability Index; SSRIs=selective serotonin reuptake inhibitors

Table 2. Concomitant medication use among completers (n=638) at baseline and Year 10. pp=percentage points. Reductions were clinically driven, not protocol-mandated. SSRIs=selective serotonin reuptake inhibitors.

Table 2. Concomitant Medication Use (n=638 Completers)

Medication	Baseline	Year 10	Change (pp)
Tramadol/Tapentadol	89.7%	5.6%	−84.0
Benzodiazepines	78.8%	5.3%	−73.5
SSRIs	77.7%	5.8%	−71.9
Gabapentinoids	31.3%	0.6%	−30.7

pp=percentage points. Reductions were clinically driven, not protocol-mandated. SSRIs=selective serotonin reuptake inhibitors

Figures

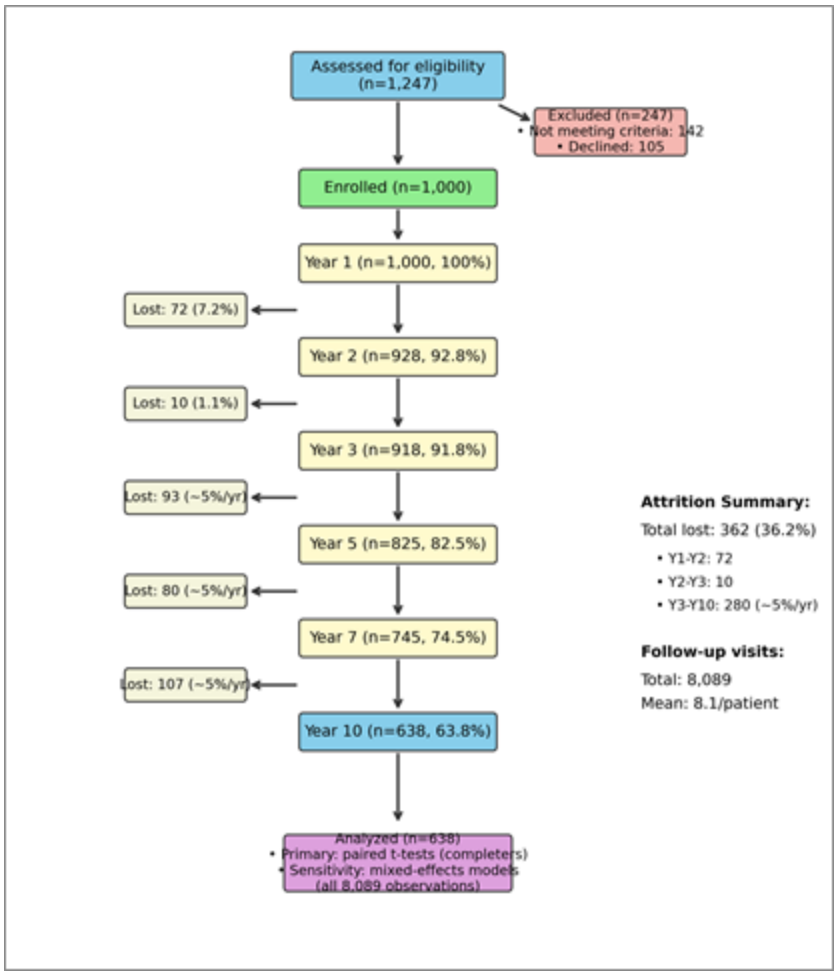


Figure 1

CONSORT flow diagram showing patient enrollment and retention over 10 years. Of 1,247 patients assessed for eligibility, 1,000 were enrolled; 638 (63.8%) completed Year 10 follow-up. Reasons for dropout are specified at each timepoint.

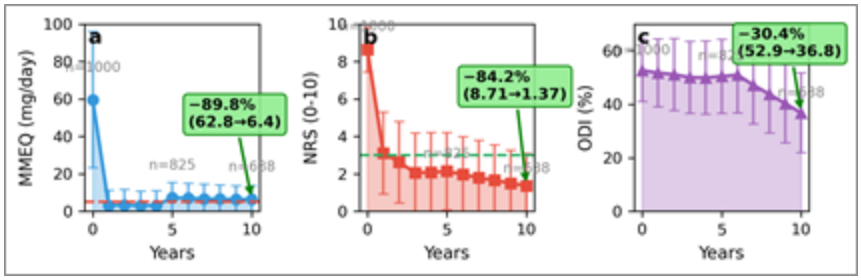


Figure 2

Primary outcomes over 10 years. (A) Opioid consumption (MMEQ); (B) Pain intensity (NRS); (C) Functional disability (ODI). Error bars represent standard deviation. Sample sizes shown at key timepoints. Annotations show change from completers' baseline to Year 10: MMEQ −89.8% (62.8→6.4), NRS −84.2% (8.71→1.37), ODI −30.4% (52.9→36.8). Note the delayed improvement in ODI relative to MMEQ and NRS.

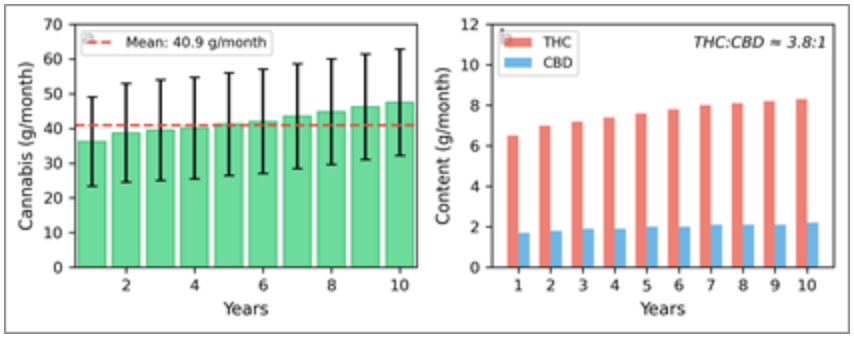


Figure 3

Cannabis dosing patterns over 10 years. (A) Total cannabis consumption (g/month); mean 40.9 g/month across Years 1–10. (B) THC and CBD content (g/month); THC:CBD ratio approximately 3.8:1. Dosing stabilized by Year 2 and remained relatively constant, with no evidence of dose escalation suggesting tolerance.

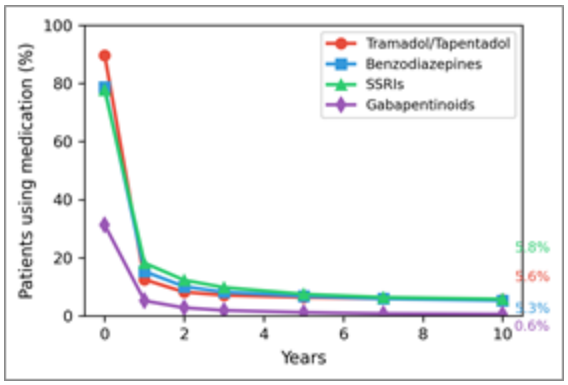


Figure 4

Concomitant medication use over 10 years among completers (n=638). Substantial polypharmacy reduction occurred: Tramadol/tapentadol 89.7% to 5.6% (−84.0 pp); Benzodiazepines 78.8% to 5.3% (−73.5 pp); SSRIs 77.7% to 5.8% (−71.9 pp); Gabapentinoids 31.3% to 0.6% (−30.7 pp). Changes were clinically driven, not protocol-mandated.

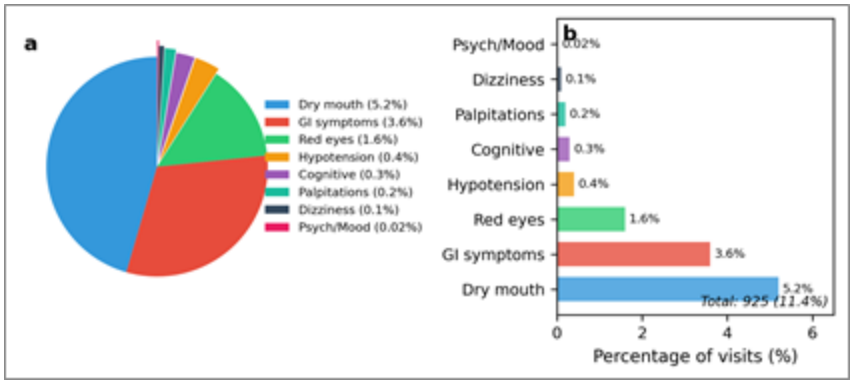


Figure 5

Adverse events across 8,089 follow-up visits. (A) Distribution by type: true tolerability events (11.4%) versus efficacy-related complaints (15.1%). (B) Most common tolerability events: dry mouth (5.2%), GI symptoms (3.6%), red eyes (1.6%), hypotension (0.4%), cognitive (0.3%), palpitations (0.2%), dizziness (0.1%). Serious psychiatric events occurred in 0.02% of visits.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CannabisCLBPStudyData.xlsx