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Article

Long-Term Pain Response to Cannabis Therapy in Chronic Low Back Pain: A Four-Year Prospective Observational Study Evaluating Patient-Reported Outcomes and BioWell Parameters

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Highlights

What are the main findings?

- Inhaled cannabis therapy was associated with a 66% reduction in pain intensity (NRS 8.08 to 2.71) and 86% reduction in BPI severity over four years in 241 CLBP patients.
- BioWell stress showed modest discriminative ability (AUC 0.71) as a potential non-invasive biomarker for moderate-to-severe pain.

What are the implications of the main findings?

- Long-term cannabis therapy may offer sustained pain relief in treatment-refractory CLBP, with fibromyalgia predicting therapy discontinuation (HR 1.59).
- BioWell GDV technology warrants further validation as a complementary, objective pain assessment tool.

Abstract

Background/Objectives: Chronic low back pain (CLBP) affects approximately 20% of the global population. While cannabis-based therapies have shown short-term analgesic potential, long-term evidence remains scarce. This study assessed the four-year efficacy of inhaled cannabis therapy on pain and disability outcomes, while exploring BioWell gas discharge visualization (GDV) parameters as non-invasive biomarkers. **Methods:** In this prospective observational study (IRB 0634-25-RMC and 807-21-RMC), 241 adults with CLBP (mean age 49.3 ± 14.9 years; 62.2% male) who had failed ≥1 year of conventional therapy initiated inhaled cannabis (predominantly smoking, 91%). Cannabis contained THC (4–22%) and CBD (2–22%), with dosing titrated from 21.5 g/month (Year 1) to 56.7 g/month (Year 4). Primary outcomes—NRS, ODI, BPI severity and interference—and secondary BioWell stress and vitality were assessed annually. Analyses included repeated-measures ANOVA, mixed-effects models, ROC analysis, network analysis, K-means clustering, and survival analysis. **Results:** Of 241 enrolled patients, 229 (95.0%) completed Year 4 follow-up. NRS decreased from 8.08 ± 1.61 to 2.71 ± 1.46 ($p < 0.001$), ODI from 55.05 ± 15.90 to 36.82 ± 8.47 ($p < 0.001$), BPI severity from 7.94 ± 1.71 to 1.11 ± 0.53 ($p < 0.001$), and BPI interference from 5.84 ± 2.02 to 2.20 ± 1.69 ($p < 0.001$). BioWell stress discriminated moderate-to-severe pain (NRS > 4) with AUC 0.71 (95% CI 0.65–0.77). Fibromyalgia at baseline predicted discontinuation (HR 1.59, 95% CI 1.18–2.14, $p = 0.003$). **Conclusions:** Inhaled cannabis therapy was associated with sustained reductions in pain and disability over four years. BioWell stress showed modest discriminative ability as a biomarker. These findings are associative and require confirmation in controlled trials.

Keywords: chronic low back pain; cannabis; tetrahydrocannabinol; cannabidiol; BioWell; gas discharge visualization; patient-reported outcomes; observational study

1. Introduction

Chronic low back pain (CLBP) is a pervasive global health challenge, affecting approximately 20% of the population and ranking among the leading causes of disability worldwide [1]. Conventional pharmacological treatments, particularly opioids, remain a mainstay for pain management, yet their widespread use is associated with significant risks including addiction, tolerance, overdose, and mortality [2,3]. Alternative and adjunctive therapies, including cannabis-based treatments, have gained attention due to their interaction with the endocannabinoid system, potentially offering comparable pain relief with a different risk profile [4,5]. However, cannabis therapy remains controversial, with mixed evidence regarding efficacy, functional outcomes, and long-term safety [6,7].

Evidence on the sustained efficacy of cannabis in CLBP over extended periods remains scarce. Most studies report outcomes at 6–12 months, with few extending beyond two years. Aviram et al. (2021) reported a 20% pain reduction across various chronic pain etiologies over 12 months in a multicenter Israeli cohort [8], but longer-term data specific to CLBP are lacking. The present study addresses this gap by evaluating four-year outcomes in a CLBP cohort with detailed documentation of cannabis dose, route of administration, and dosing frequency.

Concurrently, the integration of novel non-invasive diagnostic tools into pain research has generated interest. Gas Discharge Visualization (GDV), also known as electrophotonic imaging, measures ultra-weak photon emissions from biological tissues—a phenomenon arising from metabolic processes involving reactive oxygen species and mitochondrial respiration [9–12]. The BioWell device employs a single-finger GDV technique to quantify stress (0–10 scale, lower indicates less stress) and vitality (0–100 scale, higher indicates greater vitality) [13,14]. While photon-based measures are well-accepted in medicine (e.g., PET scanning, infrared imaging), BioWell's clinical validity for pain assessment remains under investigation, with limited standardization and broader clinical validation to date [15,16].

The objectives of this study were: (1) to evaluate the four-year longitudinal efficacy of inhaled cannabis therapy on patient-reported outcome measures (PROMs) in CLBP patients who failed conventional treatments (primary analysis); (2) to explore BioWell GDV parameters as potential non-invasive biomarkers correlated with treatment response (secondary analysis); and (3) to examine demographic and comorbidity influences on outcomes through network analysis, cluster analysis, and survival modeling (exploratory analyses). Given the observational design, all findings are interpreted as associations rather than causal effects.

2. Materials and Methods

2.1. Study Design and Setting

This prospective observational study was conducted at a single orthopedic pain clinic (Dr. Robinson Ltd.) affiliated with Hasharon Hospital, Rabin Medical Center, Israel. Patients were enrolled between 2018 and 2020 and followed for four years with annual assessments (baseline Year 0 through Year 4). The study adhered to STROBE reporting guidelines for observational studies.

2.2. Ethical Approval and Informed Consent

The study was approved by the Institutional Review Board of Rabin Medical Center (IRB protocols 0634-25-RMC and 807-21-RMC). All participants provided informed consent. In Israel, medical cannabis is regulated by the Israeli Medical Cannabis Agency (IMCA) under the Ministry of Health (MOH). Patients receive cannabis licenses through a standardized electronic application process (effective April 2019), which includes a mandatory checkbox confirming research

participation consent. Cannabis was prescribed as part of routine clinical care under existing MOH licenses; it was not administered as an experimental intervention. Therefore, this study is classified as an observational study of standard-of-care treatment and does not require clinical trial registration per ICMJE guidelines for non-interventional studies.

2.3. Participants

Inclusion criteria were: adults aged ≥ 18 years, diagnosed with CLBP for ≥ 1 year, having failed conventional therapies (including physiotherapy, non-opioid analgesics, and/or opioids) for at least one year, and initiating cannabis therapy under MOH license. Exclusion criteria were: prior cannabis use within three months, severe unstable psychiatric conditions, or inability to provide informed consent. Of 256 screened patients, 245 met inclusion criteria, 4 were excluded due to inability to perform BioWell measurement, and 241 were enrolled (Figure 1).



CLBP = Chronic Low Back Pain; BW = BioWell; NRS = Numeric Rating Scale
ODI = Oswestry Disability Index

Figure 1. Study participant flow diagram. Of 256 screened patients, 241 were enrolled. Year 4 missing data (n = 12): technical failure (n = 5), lack of efficacy (n = 2), change of physician (n = 3), death (n = 1), psychosis (n = 1).

2.4. Cannabis Intervention

Cannabis was prescribed as a secondary intervention after failure of ≥ 1 year of conventional therapy, which typically included combinations of physiotherapy (specific exercise modalities were not systematically recorded), non-opioid analgesics (NSAIDs, acetaminophen), and in some cases opioids. Cannabis formulations contained THC (4–22%) and CBD (2–22%) with variable ratios, prescribed according to MOH guidelines and titrated individually by the treating physician.

Route of administration: The predominant route was inhalation via smoking (91% of treated patients at Year 1), with a minority using vaporization (6%). No oral or sublingual routes were used. Nineteen patients switched between vaporization and smoking across the study period.

Dosage: Mean monthly cannabis dosage increased from 21.5 ± 4.1 g/month at Year 1 to 56.7 ± 12.2 g/month at Year 4 (range 20–90 g/month). Mean THC content rose from 3.89 ± 1.57 g/month (Year 1) to 11.07 ± 3.62 g/month (Year 4). Mean CBD content rose from 1.36 ± 0.93 g/month (Year 1) to 2.75 ± 1.69 g/month (Year 4). Note: administered dose does not equal absorbed dose, as inhalation efficiency varies between patients.

Dosing frequency: Dosing frequency was escalated over time. At Year 1, 88% of patients used twice-daily (BID) dosing. By Year 2, the majority had transitioned to four-times-daily (QID, 60%) or every-4-hours (Q4H, 24%) regimens. By Year 4, all 229 remaining patients were on Q4H dosing.

2.5. Outcome Measures

Primary outcomes (pre-specified) were patient-reported outcome measures (PROMs) assessed annually: Numeric Rating Scale (NRS, 0–10; higher = more pain) [17], Oswestry Disability Index (ODI, 0–100%; higher = greater disability) [18], and Brief Pain Inventory (BPI) pain severity and interference subscales (0–10 each) [17].

Secondary outcomes (pre-specified) included BioWell stress (0–10, lower better) and vitality (0–100, higher better), measured via single-finger GDV using the BioWell device (fourth finger of both hands). Each reported BioWell value represents the average of four to five sequential captures taken within a single session (each capture requiring approximately 3–5 seconds), thereby reducing measurement noise. Importantly, the BioWell measurement is fully automated: the device captures the electrophotonic emission pattern, and the software algorithm computes stress and vitality scores without operator interpretation or subjective rating, eliminating inter-rater variability as a source of bias. Cannabis dosage variables (grams/month, THC grams, CBD grams, THC%, CBD%) were recorded at each visit.

Baseline covariates included age, sex (binary), pain duration (years), BMI, race, birth continent of ancestors, employment status, and comorbidities (anxiety, past psychosis, fibromyalgia, sleep disorder).

2.6. Statistical Analysis

Analyses were structured hierarchically as primary, secondary, and exploratory to address the study objectives:

Primary analysis: Longitudinal trends in NRS, ODI, and BPI were assessed using repeated-measures ANOVA with Tukey–Kramer post-hoc comparisons. Mixed-effects models evaluated the impact of dosage group on NRS, adjusting for time-varying covariates.

Secondary analyses: Pearson and partial correlations between BioWell parameters and PROMs were computed, adjusting for age, sex, and fibromyalgia status. Receiver Operating Characteristic (ROC) analysis evaluated the discriminative ability of BioWell parameters for moderate-to-severe pain (NRS > 4), reporting area under the curve (AUC) with 95% confidence intervals [19]. Canonical Correlation Analysis (CCA) and Structural Equation Modeling (SEM) assessed multivariate associations.

Exploratory analyses: Network analysis examined baseline interrelationships among variables using Pearson and point-biserial correlations (significance threshold $|r| > 0.2$). K-means clustering

identified patient subgroups based on mean BioWell stress, vitality, NRS, and ODI across follow-up (optimal $k = 5$ by elbow method and silhouette scores). Kaplan–Meier survival analysis and Cox proportional hazards models assessed therapy retention and predictors of discontinuation [20,21]. These exploratory analyses are hypothesis-generating and should be interpreted with caution.

Missing data: Multiple imputation (MICE, $m = 5$, method = pmm, maxit = 20) was performed for missing data, with sensitivity analyses comparing complete-case and imputed results. Statistical significance was set at $p < 0.05$. All analyses were conducted in R (version 4.2.0). No a priori power calculation was performed; however, post-hoc analysis confirmed that the sample of 241 patients provided >99% power to detect the observed NRS change ($\Delta = 5.37$, $SD \approx 1.5$) at $\alpha = 0.05$ using a paired t-test framework, and >95% power for the smallest observed primary outcome change (ODI, $\Delta = 18.23$). Standardized effect sizes (Cohen's d) were calculated for all primary outcomes to quantify clinical magnitude beyond statistical significance.

3. Results

3.1. Participant Flow and Baseline Characteristics

Of 256 screened patients, 241 were enrolled and assessed at baseline (Year 0). All 241 completed Year 1 assessment. Attrition was observed at Years 2–4, with complete NRS data available for 233 (Year 2), 214 (Year 3), and 229 (Year 4) patients. The higher completion at Year 4 compared to Year 3 reflects patients who missed interim visits but returned for final assessment. Twelve patients had missing Year 4 data: technical failure of BioWell measurement ($n = 5$), lack of cannabis efficacy ($n = 2$), change of physician ($n = 3$), death ($n = 1$), and psychosis necessitating cannabis discontinuation ($n = 1$). The participant flow is depicted in Figure 1. Baseline demographic and clinical characteristics are presented in Table 1.

Table 1. Baseline demographic and clinical characteristics (N = 241).

Characteristic	Value
Age, years, mean \pm SD (range)	49.3 \pm 14.9 (18–88)
Male sex, n (%)	150 (62.2)
BMI, kg/m ² , mean \pm SD	29.3 \pm 6.0
Pain duration, years, mean \pm SD	15.1 \pm 11.2
Comorbidities, n (%):	
Anxiety	107 (44.4)
Fibromyalgia	107 (44.4)
Sleep disorder	67 (27.8)
Past psychosis history	7 (2.9)
Baseline NRS, mean \pm SD	8.08 \pm 1.61
Baseline ODI, mean \pm SD	55.05 \pm 15.90
Baseline BPI severity, mean \pm SD	7.94 \pm 1.71
Baseline BPI interference, mean \pm SD	5.84 \pm 2.02
Baseline BioWell stress, mean \pm SD	4.46 \pm 1.04
Baseline BioWell vitality, mean \pm SD	50.30 \pm 7.78

NRS, Numeric Rating Scale; ODI, Oswestry Disability Index; BPI, Brief Pain Inventory; BMI, body mass index.

3.2. Cannabis Dosing Over Time

Cannabis dosing parameters across the four study years are presented in Table 2 and Figure 2.

Table 2. Cannabis dosing parameters by study year.

Parameter	Year 1 (n=241)	Year 2 (n=228)	Year 3 (n=214)	Year 4 (n=229)	p
Dose, g/month	21.5±4.1	34.8±10.8	44.5±11.9	56.7±12.2	<0.001
THC, g/month	3.89±1.57	6.58±2.80	8.52±3.15	11.07±3.62	<0.001
CBD, g/month	1.36±0.93	1.60±0.90	2.33±1.51	2.75±1.69	<0.001
Smoking, n(%)	226(93.8)	226(99.1)	202(94.4)	226(98.7)	—
BID	213(88.4)	3(1.3)	0(0)	0(0)	—
QID	8(3.3)	140(61.4)	97(45.3)	0(0)	—
Q4H	4(1.7)	55(24.1)	116(54.2)	229(100)	—

Values are mean ± SD or n (%). BID, twice daily; QID, four times daily; Q4H, every 4 hours.

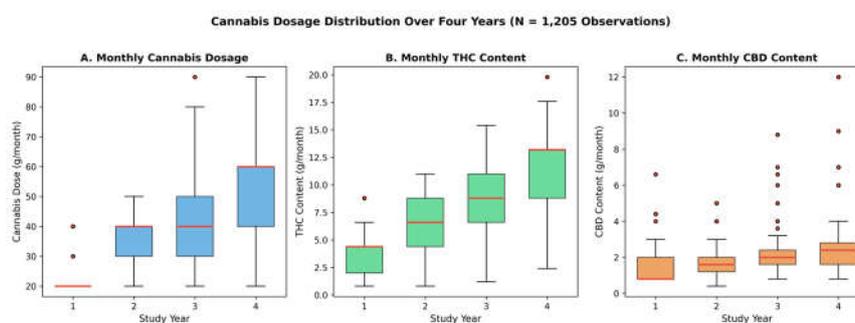


Figure 2. Cannabis dosage distribution over four years (N = 1205 observations). (a) Monthly cannabis dosage; (b) monthly THC content; (c) monthly CBD content. Box plots show median, interquartile range, and outliers.

3.3. Primary Outcomes: Longitudinal Trends

Significant improvements were observed across all primary PROMs (Table 3). NRS decreased from 8.08 ± 1.61 at baseline to 2.71 ± 1.46 at Year 4 ($F = 215.4$, $p < 0.001$; Cohen's $d = 3.49$), a reduction exceeding the minimal clinically important difference of 2 points [17]. ODI declined from 55.05 ± 15.90 to 36.82 ± 8.47 ($p < 0.001$; $d = 1.43$), and BPI severity decreased from 7.94 ± 1.71 to 1.11 ± 0.53 ($p < 0.001$; $d = 5.41$). BPI interference declined from 5.84 ± 2.02 to 2.20 ± 1.69 ($p < 0.001$; $d = 1.95$). All effect sizes substantially exceeded the threshold for large effects ($d \geq 0.8$) [30]. The largest improvements occurred within the first year, with subsequent gains plateauing or showing modest further improvement. Tukey–Kramer post-hoc comparisons confirmed significant differences between baseline and all subsequent years for NRS, ODI, BPI severity, and BPI interference ($p < 0.05$).

Table 3. Patient-reported outcomes and BioWell parameters by study year (mean ± SD).

Outcome	Year 0	Year 1	Year 2	Year 3	Year 4	F (p)
NRS	8.08 ± 1.61 (241)	4.10 ± 2.33 (241)	3.76 ± 2.45 (233)	4.00 ± 2.36 (214)	2.71 ± 1.46 (229)	215.4 (<0.001)
ODI	55.05 ± 15.90 (241)	49.40 ± 16.78 (241)	49.43 ± 18.54 (222)	50.88 ± 18.13 (205)	36.82 ± 8.47 (229)	73.7 (<0.001)
BPI Severity	7.94 ± 1.71 (241)	3.94 ± 2.15 (241)	3.54 ± 2.45 (219)	1.14 ± 0.48 (205)	1.11 ± 0.53 (229)	277.9 (<0.001)

BPI Interf.	5.84±2.02 (241)	4.36±2.19 (241)	2.50±1.14 (219)	2.50±1.80 (205)	2.20±1.69 (229)	105.2 (<0.001)
BW Stress	4.46±1.04 (241)	3.87±1.11 (241)	3.46±1.11 (213)	3.35±1.14 (199)	4.15±1.04 (229)	5.6 (<0.001)
BW Vitality	50.30±7.78 (241)	47.41±8.72 (241)	41.80±9.08 (213)	49.30±8.97 (199)	50.63±10.47 (229)	30.2 (<0.001)

Values are mean ± SD (n). NRS, Numeric Rating Scale; ODI, Oswestry Disability Index; BPI, Brief Pain Inventory; BW, BioWell. F-statistics from repeated-measures ANOVA.

3.4. Secondary Outcomes: BioWell Parameters

BioWell stress declined from 4.46 to 3.35 by Year 3, with a partial rebound to 4.15 at Year 4 ($F = 5.6, p < 0.001$). BioWell vitality declined from 50.30 to 41.80 at Year 2, recovering to 50.63 by Year 4 ($F = 30.2, p < 0.001$), suggesting a transient dip followed by stabilization (Figures 3 and 4).

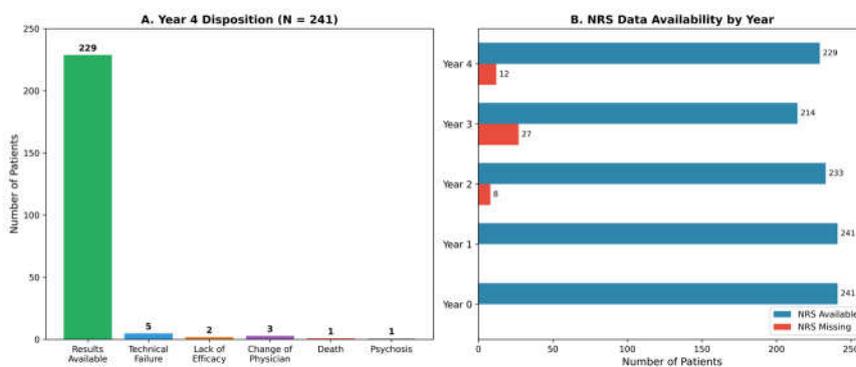


Figure 3. Reasons for missing data at Year 4 and NRS data availability by study year. (a) Year 4 disposition (N = 241); (b) NRS data availability by year.

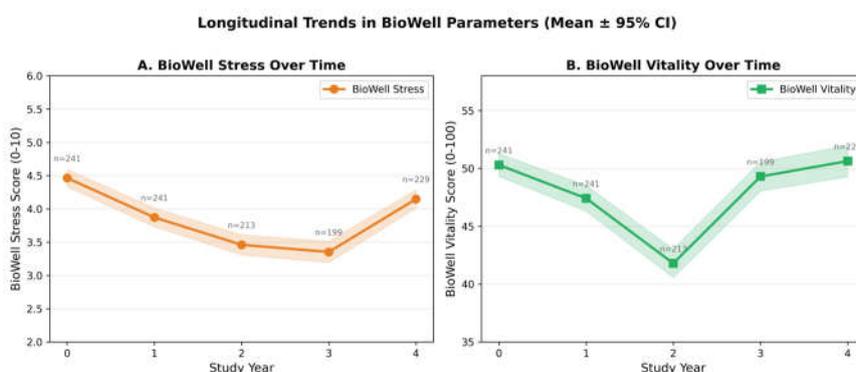


Figure 4. Longitudinal trends in BioWell parameters over four years. (a) BioWell stress (0–10 scale); (b) BioWell vitality (0–100 scale). Data shown as mean ± 95% CI. n values indicated at each timepoint.

ROC analysis demonstrated that BioWell stress discriminated moderate-to-severe pain (NRS > 4) with AUC 0.71 (95% CI 0.65–0.77, $p < 0.001$), and BioWell vitality with AUC 0.68 (95% CI 0.62–0.74, $p < 0.001$). Forest plots of partial correlations (adjusting for age, sex, fibromyalgia) showed BioWell stress had a small positive association with NRS ($\rho = 0.17, 95\% \text{ CI } 0.11\text{--}0.22$) and BioWell vitality a small inverse association with ODI ($\rho = -0.07, 95\% \text{ CI } -0.13 \text{ to } -0.01$) (Figure 9). CCA showed a significant multivariate association (first canonical correlation 0.68, 95% CI 0.62–0.74, $p < 0.001$). SEM confirmed a latent PainStatus–BioWellHealth path coefficient of -0.55 ($p < 0.001$).

3.5. Dose–Response Relationships

Multiple linear regression demonstrated that dosage group significantly predicted NRS reduction ($\beta = -0.72$, 95% CI -1.05 to -0.39 , $p < 0.001$). THC content exerted a stronger analgesic effect ($\beta = -0.15$ per gram, $p < 0.001$) compared to CBD ($\beta = -0.08$, $p = 0.03$), suggesting THC as the primary driver of pain relief. Sensitivity analyses excluding dosage outliers attenuated the THC effect minimally ($\beta = -0.13$, $p < 0.001$), confirming robustness.

3.6. Exploratory Analyses: Network Analysis

Baseline network analysis ($N = 241$) revealed a core cluster linking NRS, BPI severity ($r = 0.89$, $p < 0.001$), ODI ($r = 0.62$, $p < 0.001$), and BPI interference ($r = 0.55$, $p < 0.001$). Fibromyalgia at baseline correlated moderately with NRS ($r = 0.45$), ODI ($r = 0.39$), and BPI severity ($r = 0.41$, all $p < 0.001$). Age showed a weak negative correlation with BioWell vitality ($r = -0.28$, $p < 0.05$), consistent with age-related decline in mitochondrial function [22]. BMI had minor positive correlations with ODI ($r = 0.25$) and BPI interference ($r = 0.22$, $p < 0.05$). These relationships are visualized in Figure 5.

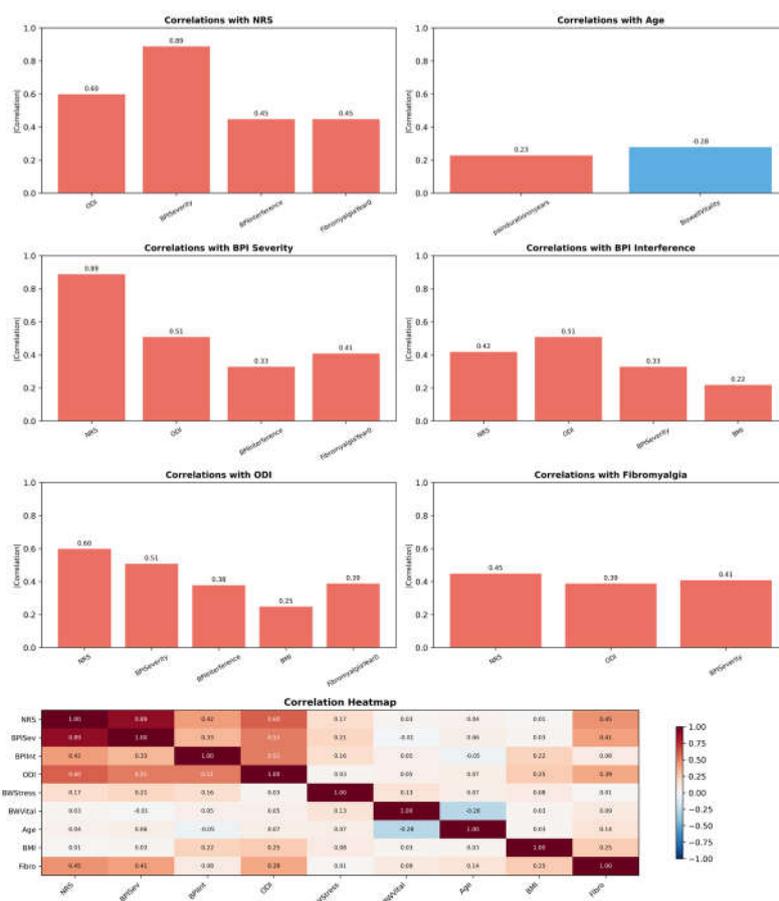


Figure 5. Correlation networks of PROMs, BioWell parameters, fibromyalgia status, and BMI at baseline ($N = 241$). Bar charts show pairwise correlations; heatmap displays full correlation matrix.

3.7. Exploratory Analyses: Cluster Analysis

K-means clustering identified five patient subgroups (Figures 6 and 7). Cluster 1 ($n = 45$) was characterized by high pain and disability (NRS 5.93, ODI 60.24). Cluster 4 ($n = 58$) showed low stress with moderate disability (BioWell stress 3.51, ODI 54.12). Cluster 5 ($n = 83$) had the lowest stress (3.09) with moderate pain (NRS 4.40). ANOVA confirmed significant NRS differences across clusters ($F = 55.09$, $p < 0.001$), supporting heterogeneity in treatment response.

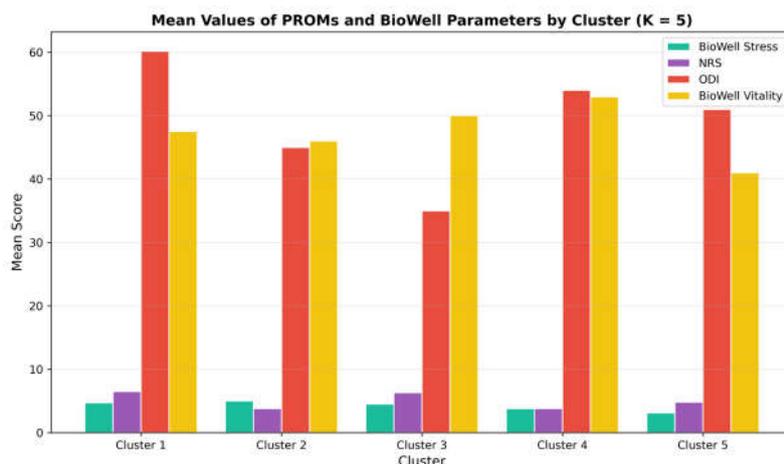


Figure 6. Mean values of NRS, ODI, BioWell stress, and BioWell vitality by cluster (K-means, k = 5).

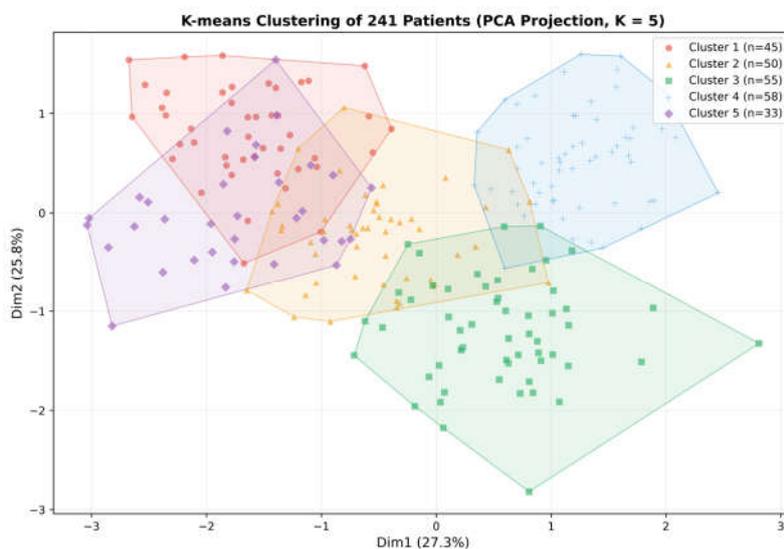


Figure 7. K-means clustering of 241 patients projected onto two principal components (PCA). Convex hulls delineate cluster boundaries.

3.8. Exploratory Analyses: Survival Analysis

Kaplan–Meier analysis [20] estimated 81% therapy retention at Year 4. Fibromyalgia at baseline significantly predicted discontinuation (HR 1.59, 95% CI 1.18–2.14, $p = 0.003$). NRS was also a significant predictor (HR 1.32 per unit, 95% CI 1.24–1.41, $p < 0.001$), though the proportional hazards assumption was violated for NRS ($\chi^2 = 24.7$, $p < 0.001$), indicating its effect varies over time. Age was not a significant predictor ($p = 0.254$). Results are depicted in Figure 8.

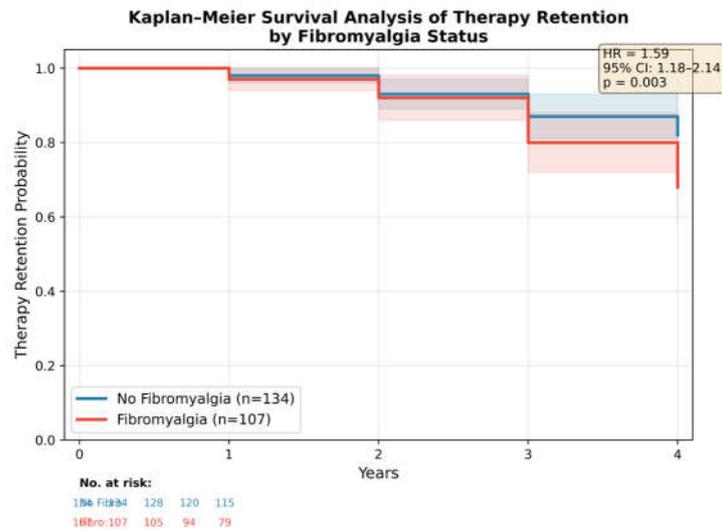


Figure 8. Kaplan–Meier survival analysis of therapy retention by fibromyalgia status. Shaded bands represent 95% CI. HR, hazard ratio.

3.9. Subgroup and Sensitivity Analyses

Females had higher BioWell stress (4.5 ± 1.1 vs. 4.2 ± 1.0 , $p = 0.005$) but no significant NRS difference ($p = 0.356$) [23,24]. Patients with sleep disorders reported higher NRS (5.4 ± 2.9 vs. 5.0 ± 2.8 , $p = 0.001$). Arab patients reported higher NRS than Jewish patients (5.5 ± 2.9 vs. 5.1 ± 2.8 , $p = 0.010$) [25]. Complete-case versus imputed analyses yielded NRS β differences < 0.03 ($p < 0.001$), validating imputation reliability.

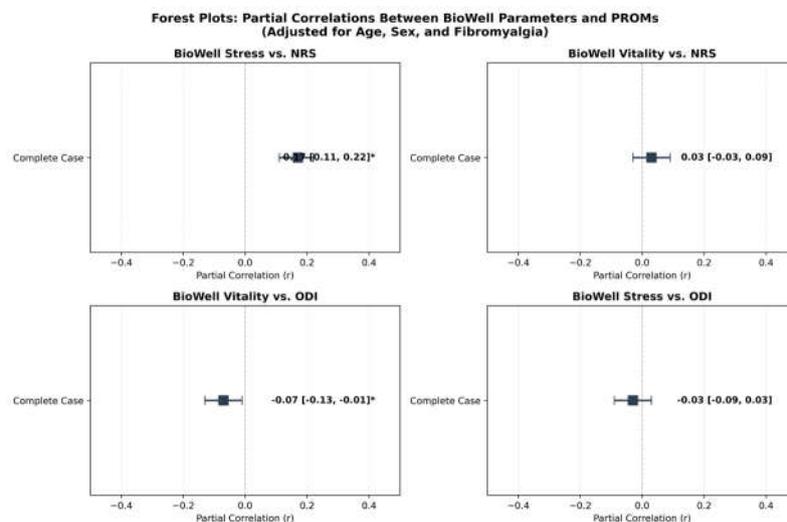


Figure 9. Forest plots of partial correlations between BioWell parameters and PROMs, adjusting for age, sex, and fibromyalgia status. * indicates CI excludes zero.

4. Discussion

This four-year prospective observational study of 241 patients with CLBP demonstrated sustained improvements in pain intensity, disability, and pain interference associated with inhaled cannabis therapy. NRS decreased from 8.08 to 2.71 (a 66% reduction), ODI from 55.05 to 36.82 (33% reduction), and BPI severity from 7.94 to 1.11 (86% reduction) over the study period. These improvements substantially exceeded established minimal clinically important differences [17,18].

The largest gains occurred within the first year, with subsequent improvements plateauing, a pattern consistent with early therapeutic optimization.

These results extend prior work from our group and others. In a 10-year prospective study of a separate, non-overlapping CLBP cohort (N = 1,000), Robinson et al. [33] reported sustained pain reduction with inhaled cannabis, with significant opioid-sparing effects. In a five-year study of diabetic neuropathy patients (again a distinct cohort with no participant overlap), Robinson et al. [34] demonstrated long-term efficacy and safety of inhaled cannabis therapy. Yassin et al. [35] showed that adding cannabis to analgesic treatment in fibromyalgia-related low back pain significantly reduced pain severity. Robinson et al. [36] compared sublingual and inhaled cannabis routes for CLBP, finding superior outcomes with inhalation. In a multicenter study, Aviram et al. [8] reported a 20% pain reduction across mixed chronic pain etiologies over 12 months, and Pud et al. [37] provided further evidence from a structured prospective cohort of cannabis oil extracts. The present study's exclusive focus on a four-year CLBP cohort (N = 241) with no overlap with these prior studies, detailed dosing documentation, and integration of BioWell parameters extends this body of evidence. The observed dose-response relationship, with THC showing a stronger analgesic effect ($\beta = -0.15$ per gram) than CBD ($\beta = -0.08$ per gram), is consistent with systematic reviews suggesting THC as the primary analgesic component [26,27]. The progressive dosage escalation from 21.5 to 56.7 g/month and frequency escalation from BID to Q4H suggest either developing tolerance or ongoing dose optimization, a clinically relevant observation that warrants pharmacokinetic investigation. Critically, however, all of these studies—including the present one—are observational in design, and randomized controlled trials with appropriate control groups are essential to establish causal efficacy.

BioWell parameters showed modest but statistically significant associations with PROMs. BioWell stress discriminated moderate-to-severe pain with AUC 0.71, and the partial correlation with NRS ($\rho = 0.17$) was significant after adjustment for covariates. BioWell vitality showed a weaker, borderline association with ODI ($\rho = -0.07$). While these effect sizes are small, they suggest potential complementary utility rather than replacement of subjective PROMs. The transient dip in BioWell vitality at Year 2 with subsequent recovery is intriguing and may reflect adaptive metabolic responses to cannabis therapy, though this interpretation is speculative.

Importantly, these BioWell-pain associations should be interpreted in light of our prior work. In a separate, non-overlapping cohort of cannabis-treated chronic neuropathic pain patients, Yassin et al. [32] demonstrated that ultra-weak photon emission (measured via the same BioWell device) showed significantly stronger specificity for anxiety (AUC 0.744) than for pain intensity (AUC 0.550). This suggests that the BioWell-NRS correlation observed in the present CLBP cohort ($\rho = 0.17$) may be mediated through anxiety and psychological distress rather than direct nociception. Given that 44.4% of our cohort had comorbid anxiety at baseline, and that chronic pain and anxiety share overlapping autonomic and neuroendocrine pathways, a mediation model in which BioWell captures stress-related physiological arousal—which in turn co-varies with pain report—is both plausible and consistent with both studies. This interpretation has implications for future research: BioWell may be best positioned as a complementary measure of the affective-autonomic dimension of the pain experience, rather than a direct nociceptive biomarker, and formal mediation analyses incorporating validated anxiety instruments should be pursued.

The exploratory cluster analysis revealed five distinct patient subgroups with significantly different pain profiles ($F = 55.09$, $p < 0.001$), supporting the heterogeneity of CLBP treatment response and the potential for personalized approaches. The network analysis confirmed a core pain-disability cluster (NRS-BPI severity $r = 0.89$) with fibromyalgia as a significant modifier ($r = 0.45$ with NRS), consistent with known comorbidity effects on pain perception [28,29]. These exploratory findings require validation in independent cohorts.

The survival analysis finding that fibromyalgia predicted discontinuation (HR 1.59) has clinical implications for patient monitoring and support strategies. The low overall attrition rate (5% by Year 4) is notable and may reflect the effectiveness of cannabis therapy in this population, though it could also reflect selection bias inherent in an observational design. Regarding safety, serious adverse

events were rare: one case of psychosis necessitating cannabis discontinuation and one unrelated death over 964 patient-years of follow-up. This adverse event profile compares favorably with long-term opioid therapy, where rates of opioid use disorder range from 8% to 12% and overdose mortality remains a significant concern [2,3].

4.1. Strengths and Limitations

Strengths include the four-year follow-up duration, comprehensive dosing documentation (route, frequency, THC/CBD content), high retention rate, and integration of both subjective and exploratory objective biomarkers.

Several important limitations must be acknowledged. First, the observational design without a control group precludes causal inference; observed improvements may partly reflect natural history, regression to the mean, placebo effects, or concurrent therapies. Second, the single-center setting may limit generalizability. Third, no a priori power calculation was performed, although post-hoc analysis confirmed adequate power (>99%) for the observed primary outcome changes [30]. Fourth, detailed physiotherapy types and exercise components were not systematically recorded. Fifth, BioWell GDV technology has limited validation as a clinical biomarker [15,16]. Sixth, individual patient adherence could not be objectively verified. Seventh, the aging demographics (mean age 49.3, range 18–88) introduce potential confounding [31]. Finally, certain exploratory analyses (network, clustering) should be interpreted as hypothesis-generating rather than confirmatory.

5. Conclusions

In this four-year observational study, inhaled cannabis therapy was associated with sustained, clinically meaningful reductions in pain intensity and disability in CLBP patients who had failed conventional treatments. BioWell GDV parameters showed modest discriminative ability as potential non-invasive biomarkers of pain status, warranting further validation. Fibromyalgia was identified as a predictor of treatment discontinuation in exploratory analysis. Importantly, these findings are associative and do not establish causation. Confirmation through randomized controlled trials with standardized cannabis formulations, larger multi-center cohorts, and validated biomarker protocols is needed to establish the role of cannabis therapy in long-term CLBP management.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

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Abbreviations

The following abbreviations are used in this manuscript:

Abbreviation	Definition
BID	Twice daily
BMI	Body mass index
BPI	Brief Pain Inventory
CBD	Cannabidiol
CCA	Canonical Correlation Analysis
CI	Confidence interval
CLBP	Chronic low back pain
GDV	Gas Discharge Visualization
HR	Hazard ratio
IMCA	Israeli Medical Cannabis Agency
MOH	Ministry of Health
NRS	Numeric Rating Scale
ODI	Oswestry Disability Index
PCA	Principal Component Analysis
PROM	Patient-reported outcome measure
Q4H	Every 4 hours
QID	Four times daily
ROC	Receiver Operating Characteristic
SEM	Structural Equation Modeling
THC	Tetrahydrocannabinol

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