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ORIGINAL RESEARCH

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Comparing the effects of medical cannabis for chronic pain patients with and without co-morbid anxiety: A cohort study

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ABSTRACT

Introduction: There is growing evidence on the efficacy of cannabis-based medicinal products (CBMPs) for chronic pain (CP). Due to the interaction between CP and anxiety, and the potential impact of CBMPs on both anxiety and CP, this article aimed to compare the outcomes of CP patients with and without co-morbid anxiety following CBMP treatment.

Methods: Participants were prospectively enrolled and categorized by baseline General Anxiety Disorder-7(GAD-7) scores, into 'no anxiety'(GAD-7 < 5) and 'anxiety'(GAD-7 ≥ 5) cohorts. Primary outcomes were changes in Brief Pain Inventory Short-Form, Short-form McGill Pain Questionnaire-2, Pain Visual Analogue Scale, Sleep Quality Scale (SQS), GAD-7 and EQ-5D-5L index values at 1, 3 and 6 months.

Results: 1254 patients (anxiety = 711; no anxiety = 543) met inclusion criteria. Significant improvements in all primary outcomes were observed at all timepoints ($p < 0.050$), except GAD-7 in the no anxiety group($p > 0.050$). The anxiety cohort reported greater improvements in EQ-5D-5L index values, SQS and GAD-7($p < 0.050$), but there were no consistent differences in pain outcomes.

Conclusion: A potential association between CBMPs and improvements in pain and health-related quality of life (HRQoL) in CP patients was identified. Those with co-morbid anxiety reported greater improvements in HRQoL.

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Cannabis; cannabidiol; tetrahydrocannabinol; pain; chronic pain; anxiety

1. Introduction

Chronic pain (CP) prevalence is estimated at 34.0% in the United Kingdom (UK), with approximately 12.0% of CP patients consequently unable to perform daily activities [1]. Despite this, CP treatment options are limited, with a paucity of evidence describing their long-term efficacy, whilst there are also known safety concerns [2]. There is subsequently increasing interest in identifying novel pharmaceuticals for CP, such as cannabis-based medicinal products (CBMPs) [3]. CBMPs are a class of medications containing phytocannabinoids, and often terpenes and flavonoids, derived from the cannabis plant. The two most abundant phytocannabinoids are Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD), which principally act on the cannabinoid receptors (CB-Rs) of the endocannabinoid system (ECS) [4–6].

CB_1-Rs are primarily expressed in the central and peripheral nervous systems, concentrated in areas associated with nociceptive processing [7–9]. CB_1-R agonism inhibits neurotransmitter release in these areas resulting in both analgesic and psychotropic effects [4,6]. CB_2-Rs are predominantly expressed in peripheral immune cells, where they modulate inflammatory cytokines [5,10,11]. THC is a partial agonist for CB_1-R and CB_2-R [4]. CBD inhibits hydrolysis of endogenous CB-R agonists, thus increasing constitutive activation, whilst also being a noncompetitive negative allosteric modulator of CB_1-Rs [9,12–14]. Phytocannabinoid analgesic effects are also thought to be mediated through non-CB-Rs, including transient receptor potential cation channel V1, G protein-coupled receptor 55, peroxisome proliferator-activated receptor–gamma, opioid, and serotonin receptors [15–17].

There is increasing clinical evidence on the efficacy of CBMPs for CP [18–27], with a recent meta-analysis concluding that CBMPs are associated with a small, yet clinically significant, reduction in pain severity [28]. However, conclusions are variable due to the heterogeneity and low quality of primary research on CBMPs, with other studies questioning their efficacy and safety [29–32], warranting further research.

There is limited evidence on the factors that predict which CP patients are most likely to benefit from CBMPs. A pertinent

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group to consider is those with co-morbid anxiety, which frequently co-occurs with CP [33]. For example, anxiety is at least twice as prevalent in those with chronic neck or back pain [34]. Both CBD and THC are both thought to have anxiolytic effects, however clinical studies to date have been limited and of low quality [32,35–37]. The relationship between anxiety and CP is complex and bidirectional, as described by the biopsychosocial model of pain, in which anxiety is both a cause and consequence of CP [38,39]. Co-occurrence of both conditions has been shown to reduce anxiety treatment efficacy and worsen pain-related outcomes [33,40,41]. A potential underlying mechanism linking anxiety and CP includes central sensitization, in which nociceptor responsiveness is increased, resulting in hyperalgesia [42–47]. Early evidence suggests cannabinoids may attenuate central sensitization-induced hyperalgesia [48–52]. Another suggested mechanism is catastrophizing, in which the threat posed by actual or anticipated stimuli is heightened and associated with negative pain-related thoughts [53]. Although catastrophizing is a distinct construct that independently influences pain outcomes [54–56], it is associated with anxiety [53–55,57–59], and originates from a maladaptive cognitive style typical in anxiety patients [53,60,61]. Both chronic pain and anxiety are heterogenous conditions with complex neurobiological underpinnings, hence it must be considered that a single therapeutic may not prove to be a successful treatment in all individuals, with enhanced effects in select patients [62,63].

The primary aim of this study was to therefore compare pain-specific patient-reported outcome measure (PROM) changes between CP patients with and without co-morbid anxiety. Secondary aims included comparing general health-related quality of life (HRQoL) PROMs, adverse event (AE) incidence, and opioid medication consumption changes between cohorts.

2. Methods

2.1. Study design

A prospective observational cohort study comparing the effects of CBMPs for CP patients with and without co-morbid anxiety was performed utilizing data from the UK Medical Cannabis Registry (UKMCR). All participants provided informed written consent prior to enrollment. In accordance with the NHS Health Research Authority and Research Ethics Committee's guidance [64], this study did not require formal ethical approval. However, the UKMCR has received approval from the South West–Central Bristol Research Ethics Committee (Ref: 22/SW/0145). This study was reported utilizing the STROBE guidelines [65]. The ROBINS-I tool was used for assessment of quality and risk of bias [66].

The primary outcome was to compare pain-specific PROM changes from baseline to follow-up between CP patients with and without anxiety. The secondary outcomes included comparing general HRQoL PROMs, AE incidence, and oral morphine equivalent (OME) change between cohorts. Subgroup analysis according to anxiety severity was performed.

2.2. Setting and participants

The UKMCR, established in 2019, is privately owned and managed by Sapphire Medical Clinics. It is the first registry to prospectively record pseudonymized data of UK and Channel Islands patients prescribed CBMPs. Previously published data from the UKMCR has concluded that CBMPs are associated with improvements in pain in CP patients, anxiety in GAD patients, and improvements in HRQoL in both groups [67,68]. Patients complete baseline questionnaires remotely prior to initial consultation and during treatment, enabling participant follow-up. Baseline patient demographics are completed during initial consultation by the treating physician. Adverse events can be reported at time of occurrence or contemporaneously utilizing an online questionnaire, or by clinicians during a follow-up visit if otherwise unreported prior to that. All patients are assigned a primary diagnosis following clinician assessment, for which CBMP treatment is indicated, as well as secondary and tertiary indications if present.

Inclusion criteria for this study were participants where CP was the primary indication for CBMP treatment. Exclusion criteria were those without completion of a baseline PROMs and those enrolled in the UKMCR for <1 month at the time of data extraction (15 February 2022). There were no further reasons for exclusion. Participants were consecutively enrolled into the study. The recruitment period for participants and period of baseline data collection was from the 1 December 2021 until the 15 January 2022.

Baseline Generalized Anxiety Disorder Assessment (GAD-7) scores classified participants into 'no anxiety' (GAD-7 < 5) and 'anxiety' (GAD-7 ≥ 5) cohorts. The thresholds of ≥5, ≥10, and ≥15 were used to determine mild, moderate, and severe anxiety cohorts for subgroup analysis [69,70].

2.3. Data collection

Demographic data, including age, gender, medical history, height, and weight, were collected at baseline. Occupation was recorded using the International Standard Classification of Occupations [71]. Comorbidity incidence was documented, and the Charlson comorbidity index, a commonly used prognostic tool in patient registries, was calculated [72,73]. The presence of an intellectual disability was not recorded.

Tobacco, alcohol, and cannabis consumption were documented. To quantify prior cannabis consumption, a novel, but unvalidated metric of 'gram years' (mean cannabis consumption per day (grams) × years of use) was calculated [74]. All CBMP prescriptions met Good Manufacturing Practice (GMP) standards [75], and were recorded and analyzed for their administration route, cannabinoid contents, and dosages. If baseline data were missing post-questionnaire completion and clinician augmentation, research team members contacted participants to try and collect outstanding data retrospectively.

As the gold-standard of CP assessment is self-reporting [76], all participants were prompted to complete validated pain-specific and general HRQoL PROMs at baseline (except for the patient global impression of change (PGIC)) and 1,

3, and 6 months. The PROMs utilize numerical rating scales (NRS) and visual analog scales (VAS) to measure responses [76,77]. The following PROMs were collected:

2.3.1. Pain-specific

2.3.1.1. Brief pain inventory short-form (BPI). A two-part NRS which uses 11 descriptors to create a pain severity and interference subscale with scores from 0 (no pain/interference) to 10 (worst pain/complete interference) [78].

2.3.1.2. Short-form mcgill pain questionnaire (SF-MPQ-2). An NRS that evaluates the severity and character of neuropathic and non-neuropathic pain. The SF-MPQ-2 uses 22 descriptors to assess pain within four major categories: continuous, intermittent, neuropathic, and affective. Each descriptor is scored 0 (no pain) to 10 (worst pain). The score for each category is the mean of the specific descriptors within that category, whilst the overall pain score is the mean of all 22 descriptors [79,80].

2.3.1.3. VAS-pain. A VAS that evaluates pain intensity using a 10 cm line, anchored by no pain and worst pain, corresponding to a score between 0 and 10 [76,77]. The minimally important clinical difference in pain severity is 1 cm [81].

2.3.2. HRQoL-related

2.3.2.1. EQ-5D-5L. An NRS measuring HRQoL across five domains (mobility, self-care, usual activity, pain/discomfort, anxiety/depression) with five severity levels ranging from 0 (no problems) to 5 (extreme problems) [82]. The domains and accompanying severity levels are combined, generating a 5-digit code corresponding to 1 of 3125 health states, which are mapped to EQ-5D-5L index values specific to the UK [83]. Index scores range from <0 (health status worse than death) to 1 (full health) [82,83].

2.3.2.2. GAD-7. An NRS that screens for and assesses the severity of GAD. Participants are asked how often they have been bothered by the 7 core GAD symptoms in the last two weeks, on a scale of 0 (not at all) to 3 (nearly every day), generating an overall score from 0 to 21 [69,70].

2.3.2.3. Single-item sleep quality (SQS). An NRS that assesses sleep quality over the past week, utilizing a range from 0 (excellent) to 10 (terrible) [84].

2.3.2.4. PGIC. A 7-point NRS ascertaining participants' perception of change following treatment, therefore no baseline score is calculated. Options range from very much worsened to very much improved [85,86].

2.4. Oral morphine equivalents (OME)

Patients prescribed opioids at baseline or at any time point during follow-up were identified. Total OME doses per day were calculated at baseline and end of follow-up. OME doses were calculated using the British National Formulary (BNF) and Royal College of Anesthetists conversion factors [87,88].

2.5. Adverse events

AEs were self-reported by patients via electronic reporting or documented by clinicians during routine follow-ups. AEs were stratified according to The Common Terminology Criteria for AEs version 4.0 [89].

2.6. Statistical analysis

Normality of continuous variables was tested using Shapiro–Wilk tests. Parametric data were presented as a mean (±standard deviation) and nonparametric as a median (interquartile range (IQR) (Q1-Q3)). Clinicopathological characteristics of each cohort were compared using two-tailed independent t-tests for parametric data or Mann–Whitney U-tests for nonparametric data. When comparing categorical parameters, Chi-Squared Tests were utilized, and for statistically significant p-values, Bonferroni-corrected post-hoc analysis (PH) using adjusted residuals was performed [90].

As all baseline PROMs were nonparametric, Wilcoxon Signed-Rank tests were used to assess for change from baseline to follow-up within each cohort. To compare the relative changes between the two cohorts, Mann-Whitney U tests were used.

The median total OME dose over the studied period was calculated for each cohort at baseline and end of follow-up and compared using the Wilcoxon signed-rank test, and a Mann-Whitney U-test was used to compare the change between the cohorts. The frequency of AEs was reported utilizing descriptive statistics, whilst the proportion of patients who experienced an AE in either cohort was compared using a Chi-Squared test.

Univariate and multivariate logistic regression models were conducted to calculate the associated odds ratios (ORs) and corresponding 95% confidence intervals (95% CI) for independent variables and their association with improved BPI pain severity and interference, and AE likelihood.

For subgroup analysis according to anxiety severity, categorical data was analyzed using Chi-Squared Tests with PH [90]. Nonparametric data utilized Kruskal–Wallis tests with Dunn's PH. Continuous parametric data utilized One-Way ANOVA tests with Tukey's honestly significant difference PH and correction [91].

All PROMs analysis was Bonferroni-corrected to reduce the family-wise error rate.

Statistical significance was defined as $p < 0.050$. All statistical analysis was conducted using SPSS Statistics (version:28.0.0.0 IBM SPSS Inc., [New York, IL], USA) [92], and figures were produced using GraphPad Prism 9 (version:8.0.0 for Windows, GraphPad Software, San Diego, California USA) [93].

3. Results

At the time of data extraction, 3546 patients were registered on the UKMCR. 2292 patients (64.6%) were excluded: those without a baseline PROM completed (n = 443; 12.5%), enrolled for <1 month (n = 270; 7.6%), and without CP (n = 1579; 44.5%). Therefore, 1254 participants were included in analysis, with (n = 711; 56.7%) and without (n = 543; 43.3%) anxiety at

baseline. The anxiety cohort consisted of participants with mild (n = 322; 25.7%), moderate (n = 201; 16.0%), and severe (n = 188; 15.0%) anxiety. The median follow-up of the participants was 9 months (IQR: 6–12 months).

3.1. Baseline demographics

Table 1 displays baseline demographic details for both cohorts. The female:male ratio was higher in the no anxiety (1:1.4) compared to anxiety (1:1.1) cohort (p = 0.026). The mean age of the no anxiety cohort (47.0 ± 14.9 years) was higher than the anxiety cohort (44.8 ± 14.0 years; p = 0.006). Employment status differed between the cohorts (p < 0.001), with most of the no anxiety cohort being employed (n = 288; 53.1%) whilst the majority of the anxiety cohort were unemployed (n = 365; 51.3%). The most common indication for treatment in both cohorts was chronic non-cancer pain (n = 399; 73.5% and n = 512; 72.0%). For secondary and tertiary treatment indications (if any), see *Appendix A*.

The median Charlson comorbidity index was 1.0 (IQR:0.0–6.0) for both cohorts. There were no differences in comorbidity incidence between the two cohorts besides depression/anxiety (p < 0.001) and leukemia (p = 0.047) (*Appendix B*). For demographics, occupations, and comorbidities according to anxiety severity, see *Appendix C* and *D*.

Table 2 displays tobacco, alcohol, and cannabis consumption for both cohorts. Tobacco status, specifically the proportion of current smokers, differed between the no anxiety (n = 122; 22.5%) and anxiety cohort (n = 233; 31.4%; p < 0.001). Median alcohol consumption was higher in the no anxiety cohort (1.0; IQR:0.0–6.0 vs 0.0; IQR:0.0–4.0 units, respectively; p = 0.006). There was no difference between the proportion of patients in each cohort who were cannabis users at baseline, previous users, or cannabis naive (p = 0.450). For analysis according to anxiety severity, see *Appendix E*.

3.2. CBMP details

Table 3 displays CBMP details for both cohorts. Most participants in the no anxiety (n = 442; 85.5%) and anxiety (n = 568; 86.7%) cohort were prescribed both CBD and THC. The most common administration route for both cohorts was a combination of sublingual/oral formulations and vaporized flower (n = 227; 44.4% and n = 330; 50.4%, respectively). There were no significant differences in the median prescribed dose of CBD (p = 0.082) and THC (p = 0.591) between either cohort. Across both cohorts, for those prescribed both sublingual/oral formulations and vaporized flower: the median THC dose contribution from the sublingual/oral formulations was 20.0 (IQR:10.0–20.0)mg/day and the median CBD dose contribution was 20.0 (IQR: 20.0–20.0)mg/day, whilst the median THC dose contribution from the vaporized flowers was 100.0 (IQR:100.0–200.0; 100.0–195.0)mg/day and the median CBD dose contribution was 0.5 (IQR: 0.0–5.0)mg/day. The most common CBMP therapies were Adven® 20 THC oil, Adven® 50 CBD oil, Adven® EMT1 19% THC flower (Curaleaf International, Guernsey, UK). For analysis according to anxiety severity, see *Appendix F*.

3.3. Patient-Reported Outcome Measures

1018 participants (no anxiety n = 444; anxiety n = 574) were included in PROMs analysis, as 236 (18.8%) participants (no anxiety n = 99; 18.2% and anxiety n = 137; 19.3%) did not complete any follow-up PROMs.

Table 4 displays paired median baseline and follow-up (1, 3, and 6 months) scores for the BPI, SF-MPQ-2, VAS-PAIN, EQ-5D-5L, GAD-7, SQS PROMs, and solely follow-up scores for the PGIC for both cohorts. Significant improvements from baseline were observed at 1, 3, and 6 months for all PROMs in the anxiety cohort and most in the no anxiety cohort (p < 0.050). Whilst the median GAD-7 scores for the no anxiety cohort were the same at baseline, and 1, 3, and

Table 1. Baseline demographic details of study participants (n = 1254).

	n (%)/Mean (± S.D)/Median (IQR)		
Baseline Demographic Details	No Anxiety (n = 543)	Anxiety (n = 711)	p-value
Gender			0.026* PH: ns
Female	230 (42.4%)	346 (48.7%)	
Male	313 (57.6%)	365 (51.3%)	
Age (years)	47.0 (**±14.9**)	44.8 (±14.0)	0.006**
Body Mass Index (kg/m^2)	27.3 (**±7.1**)	27.6 (**±6.8**)	0.502
Employment Status			<0.001*** PH: Unemployed (p < 0.001***), Employed (p < 0.001***)
Employed	288 (53.1%)	288 (40.5%)	
Unemployed	203 (37.4%)	365 (51.3%)	
Undefined	52 (9.6%)	58 (8.2%)	
Pain Etiology			0.669
Cancer Pain	5 (0.9%)	10 (1.4%)	
Chronic Non-Cancer Pain	399 (73.5%)	512 (72.0%)	
Complex Regional Pain Syndrome	3 (0.6%)	9 (1.3%)	
Ehlers-Danlos Syndromes	35 (6.4%)	45 (6.3%)	
Neuropathic Pain	101 (18.6%)	135 (19.0%)	
Charlson Comorbidity Index	1.0 (0.0–6.0)	1.0 (0.0–6.0)	0.769

*Abbreviations: IQR = Interquartile Range, n = Number of Participants, ns = Non-Significant, PH = Post-Hoc Analysis, S.D = standard deviation. Missing Data: Body Mass Index data was missing in the no anxiety (n = 64) and anxiety cohort (n = 68). The employment status category 'unemployed' also includes those who were retired, and the category 'undefined' includes students, minors, and those who had occupation data missing. Significant differences are denoted by asterixis (*p < 0.050, **p < 0.010, ***p < 0.001).*

Table 2. Tobacco, alcohol, and cannabis consumption of study participants (n = 1254).

Tobacco, Alcohol and Cannabis Consumption	*n (%)/Median (IQR)* No Anxiety (n = 543)	Anxiety (n = 711)	p-value
Tobacco Status			0.001** PH: Current Smokers (p < 0.001)
Current Smoker	122 (22.5%)	223 (31.4%)	
Pack Years	12.0 (5.0–20.0)	12.0 (6.0–25.0)	0.521
Ex-Smoker	221 (40.7%)	275 (38.7%)	
Pack Years	10.0 (4.0–17.0)	10.0 (5.0–20.0)	0.018*
Nonsmoker	200 (36.8%)	213 (30.0%)	
Weekly Alcohol Consumption (units)	1.0 (0.0–6.0)	0.0 (0.0–4.0)	0.006**
Cannabis Status			0.450
Current User	278 (51.2%)	381 (53.6%)	
Grams Consumed per Day Currently (g/day)	1.0 (0.6–2.0)	1.0 (0.7–2.0)	0.058
Lifetime Quantity of Cannabis Consumed (gram years)	7.0 (2.0–20.0)	10.0 (3.0–22.0)	0.140
Ex-user	71 (13.1%)	100 (14.1%)	
Lifetime Quantity of Cannabis Consumed (gram years)	2.0 (1.0–10.0)	3.5 (1.0–10.0)	0.957
Never Used	194 (35.7%)	230 (32.3%)	
Frequency of Cannabis Consumption for Current Users			0.930
• Every Day	233 (83.8%)	318 (83.5%)	
• Every Other Day	22 (7.9%)	28 (7.3%)	
• 1–2 Times per Week	13 (4.7%)	22 (5.8%)	
• >Once per Month	3 (1.1%)	4 (1.0%)	
• per Month	4 (1.4%)	3 (0.8%)	

*Abbreviations: IQR = Interquartile Range, n = Number of Participants, ns = Non-Significant, PH = Post-Hoc Analysis. Missing Data: Pack year data was missing in the no anxiety (n = 3) and anxiety cohort (n = 3). Alcohol Consumption data was missing in the no anxiety (n = 10) and anxiety (n = 7) cohort. Grams Consumed per Day Currently data was missing in the no anxiety (n = 1) and anxiety cohort (n = 4). Lifetime quantity of cannabis consumed data was missing in the no anxiety (n = 1) and anxiety (n = 4) cohort. Frequency of Cannabis Consumption data was missing in the no anxiety (n = 3) and anxiety (n = 5) cohort. Significant differences are denoted by asterixis (*p < 0.050, **p < 0.010, ***p < 0.001).*

Table 3. Details of cannabis-based medicinal product (CBMP) prescribed for study participants (n = 1166).

CBMP Details	*n (%)/Median (IQR)* No Anxiety (n = 511)	Anxiety (n = 655)	p-value
Cannabinoid Contents			0.981
Number of Participants Prescribed CBD Only	15 (2.9%)	19 (2.9%)	
Number of Participants Prescribed THC Only	54 (10.6%)	68 (10.4%)	
Number of Participants Prescribed both CBD and THC	442 (86.5%)	568 (86.7%)	
Administration Route			0.117
Number of Participants using Sublingual/Oral Formulations Only	198 (38.7%)	221 (33.7%)	
Number of Participants using Vaporized Flower Only	86 (16.8%)	104 (15.9%)	
Number of Participants using both Sublingual/Oral Formulations and Vaporized Flower	227 (44.4%)	330 (50.4%)	
Dosage			
Median (IQR) CBD Dosage (mg/day)	20.0 (15.0–25.5)	20.0 (20.0–30.0)	0.082
Median (IQR) THC Dosage (mg/day)	110.0 (20.0–200.0)	110.0 (20.0–195.0)	0.591

*Abbreviations: CBD = Cannabidiol, CBMP = Cannabis-Based Medicinal Product, IQR = Interquartile Range, n = Number of Participants, THC = Δ^9Tetrahydrocannabinol. Missing Data: CBMP prescription data was missing in the no anxiety (n = 32) and anxiety (n = 56) cohorts. Significant differences are denoted by asterixis (*p < 0.050, **p < 0.010, ***p < 0.001).*

6 months (median = 1.0; IQR = 0.0–3.0; p < 0.050) there was a statistically significant change, indicating worsening anxiety. There were no significant changes in the no anxiety cohorts' EQ-5D-5L anxiety/depression score at 3 and 6 months and self-care at 1 and 6 months (p > 0.050). For analysis according to anxiety severity, see *Appendix G*.

Subsequently, Table 5 compares median PROM score changes from baseline to each time point between the cohorts. Patients with comorbid anxiety displayed greater improvements in anxiety, sleep, and general HRQoL at all time points as assessed by the GAD-7, SQS, EQ-5D-5L index value, and EQ-5D-5 L domains (p < 0.050), except EQ-5D-5L mobility and self-care at 1 and 3 months (p > 0.050). The results across the pain-specific PROMs were inconsistent.

3.3.1. Subgroup Analysis

When comparing median PROM score changes between the no anxiety and three anxiety severities using post-hoc analysis, 39 statistically significant differences were observed, all favoring greater PROM improvements in individuals with more severe anxiety (p < 0.050). 23 (59.0%) of the differences occurred between the no versus severe anxiety cohorts, 11 (28.2%) between the no versus moderate groups, and 5 (12.8%) between the no versus

Table 4. Paired baseline and follow-up patient-reported outcome measures of study participants at 1, 3, and 6 months (n = 1018).

			No Anxiety				Anxiety			
				Median (IQR)				*Median (IQR)*		
Patient Reported Outcome Measure		Follow Up (month)	n	Scores at Baseline	Scores at Follow-Up	p-value	n	Scores at Baseline	Scores at Follow-Up	p-value
Pain-Specific PROMs	BPI Pain Interference	1	413	5.6 (3.9–7.3)	4.7 (2.9–6.4)	<0.001***	542	7.4 (6.0–8.7)	6.3 (4.6–7.7)	<0.001***
		3	292	5.4 (3.7–7.0)	3.9 (2.0–6.0)	<0.001***	343	7.4 (6.0–8.7)	6.0 (4.1–7.4)	<0.001***
		6	197	5.1 (3.4–6.6)	4.3 (2.0–5.7)	<0.001***	186	7.2 (5.4–8.6)	5.3 (3.7–7.2)	<0.001***
	BPI Pain Severity	1	413	5.3 (4.0–6.5)	5.0 (3.3–6.0)	<0.001***	542	6.3 (5.0–7.3)	5.5 (4.3–6.5)	<0.001***
		3	292	5.0 (3.8–6.3)	4.5 (2.8–5.8)	<0.001***	343	6.0 (5.0–7.0)	5.0 (3.8–6.3)	<0.001***
		6	197	5.0 (3. 5–6.3)	4.3 (2.5–5.8)	<0.001***	186	5.9 (4.5–7.0)	5.0 (3.8–6.1)	<0.001***
	SF-MPQ-2 Affective Pain	1	403	3.5 (1.5–5.3)	2.3 (1.0–4.5)	<0.001***	525	5.5 (3.5–7.3)	4.3 (2.4–6.3)	<0.001***
		3	282	3.0 (1.3–5.0)	2.0 (0.7–4.0)	<0.001***	337	5.3 (3.3–7.0)	3.8 (1.8–5.8)	<0.001***
		6	189	2.5 (1.0–4.8)	1.8 (0.3–3.6)	<0.001***	183	5.0 (3.3–6.8)	3.3 (1.5–5.0)	<0.001***
	SF-MPQ-2 Continuous Pain	1	403	4.7 (3.0–6.7)	3.8 (2.0–5.8)	<0.001***	525	6.0 (4.5–7.5)	5.2 (3.5–6.7)	<0.001***
		3	282	4.7 (2.7–6.5)	3.7 (1.5–5.7)	<0.001***	337	6.0 (4.5–7.4)	4.8 (3.0–6.3)	<0.001***
		6	189	4.3 (2.3–5.9)	2.7 (1.3–5.3)	<0.001***	183	6.0 (4.2–7.2)	4.5 (2.7–6.3)	<0.001***
	SF-MPQ-2 Intermittent Pain	1	403	3.7 (1.7–5.8)	3.2 (1.3–5.0)	<0.001***	525	5.2 (3.3–7.0)	4.3 (2.2–6.0)	<0.001***
		3	282	3.5 (1.5–5.7)	2.5 (0.8–4.8)	<0.001***	337	5.2 (3.3–6.8)	3.8 (1.8–5.9)	<0.001***
		6	189	3.3 (1.3–5.2)	2.2 (0.7–4.7)	<0.001***	183	5.2 (3.0–6.7)	3.5 (1.7–5.7)	<0.001***
	SF-MPQ-2 Neuropathic Pain	1	403	2.5 (1.0–4.2)	2.0 (0.7–4.0)	<0.001***	525	3.7 (2.0–5.5)	3.0 (1.5–4.8)	<0.001***
		3	282	2.3 (0.8–4.2)	1.7 (0.5–3.7)	<0.001***	337	3.7 (2.0–5.3)	2.8 (1.1–4.7)	<0.001***
		6	189	2.3 (0.8–3.8)	1.5 (0.3–3.3)	<0.001***	183	3.5 (1.8–5.2)	2.7 (1.0–4.2)	<0.001***
	SF-MPQ-2 Overall Pain Score	1	403	3.7 (2.0–5.3)	3.0 (1.5–4.6)	<0.001***	525	5.1 (3.6–6.4)	4.1 (2.7–5.7)	<0.001***
		3	282	3.5 (1.9–5.0)	2.5 (1.1–4.5)	<0.001***	337	5.0 (3.6–6.3)	3.7 (2.3–5.3)	<0.001***
		6	189	3.3 (1.7–4.7)	2.0 (0.8–4.3)	<0.001***	183	4.9 (3.5–6.3)	3.5 (2.0–4.9)	<0.001***
	VAS-Pain	1	409	7.0 (5.0–8.0)	6.0 (4.0–7.0)	<0.001***	530	8.0 (6.0–8.0)	7.0 (5.0–8.0)	<0.001***
		3	286	7.0 (5.0–8.0)	5.0 (3.0–7.0)	<0.001***	340	7.0 (6.0–8.0)	6.0 (4.0–8.0)	<0.001***
		6	191	7.0 (5.0–8.0)	5.0 (3.0–7.0)	<0.001***	184	7.0 (6.0–8.0)	6.0 (4.0–7.0)	<0.001***
HRQoL-Related PROMs	EQ-5D-5L Pain and Discomfort	1	433	3.0 (3.0–4.0)	3.0 (2.0–4.0)	<0.001***	564	4.0 (3.0–5.0)	3.0 (3.0–4.0)	<0.001***
		3	303	3.0 (3.0–4.0)	3.0 (2.0–3.0)	<0.001***	358	4.0 (3.0–4.0)	3.0 (2.0–4.0)	<0.001***
		6	208	3.0 (3.0–4.0)	3.0 (2.0–3.0)	<0.001***	201	4.0 (3.0–4.0)	3.0 (2.0–4.0)	<0.001***
	EQ-5D-5L Anxiety and Depression	1	433	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.007**	564	3.0 (2.0–4.0)	2.0 (2.0–3.0)	<0.001***
		3	303	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.415	358	3.0 (2.0–4.0)	2.0 (2.0–3.0)	<0.001***
		6	208	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.120	201	3.0 (2.0–3.0)	2.0 (2.0–3.0)	<0.001***
	EQ-5D-5L Mobility	1	433	3.0 (2.0–4.0)	2.0 (1.0–3.0)	<0.001***	564	3.0 (2.0–4.0)	3.0 (2.0–4.0)	<0.001***
		3	303	3.0 (2.0–3.0)	2.0 (1.0–3.0)	<0.001***	358	3.0 (2.0–4.0)	3.0 (2.0–4.0)	<0.001***
		6	208	3.0 (2.0–3.0)	2.0 (1.0–3.0)	0.002**	201	3.0 (2.0–4.0)	3.0 (2.0–3.0)	<0.001***
	EQ-5D-5L Self Care	1	433	2.0 (1.0–3.0)	2.0 (1.0–3.0)	0.140	564	2.0 (1.0–3.0)	2.0 (1.0–3.0)	0.001**
		3	303	2.0 (1.0–3.0)	1.0 (1.0–2.0)	0.012*	358	2.0 (1.0–3.0)	2.0 (1.0–3.0)	<0.001***
		6	208	2.0 (1.0–3.0)	2.0 (1.0–2.8)	0.527	201	2.0 (1.0–3.0)	2.0 (1.0–3.0)	<0.001***
	EQ-5D-5L Usual Activities	1	433	3.0 (2.0–4.0)	2.0 (2.0–3.0)	<0.001***	564	3.0 (3.0–4.0)	3.0 (2.0–3.0)	<0.001***
		3	303	3.0 (2.0–3.0)	2.0 (1.0–3.0)	<0.001***	358	3.0 (3.0–4.0)	3.0 (2.0–4.0)	<0.001***
		6	208	2.0 (2.0–3.0)	2.0 (2.0–3.0)	0.002**	201	3.0 (2.0–4.0)	2.0 (2.0–3.0)	<0.001***
	EQ-5D-5L Index Value	1	433	0.5 (0.3–0.7)	0.6 (0.4–0.7)	<0.001***	564	0.3 (0.0–0.5)	0.5 (0.3–0.6)	<0.001***
		3	303	0.6 (0.3–0.7)	0.6 (0.5–0.8)	<0.001***	358	0.3 (0.0–0.5)	0.5 (0.3–0.64	<0.001***
		6	208	0.6 (0.3–0.7)	0.6 (0.5–0.8)	<0.001***	201	0.3 (0.1–0.5)	0.6 (0.3–0.6)	<0.001***
	GAD-7	1	438	1.0 (0.0–3.0)	1.0 (0.0–3.0)	0.031*	569	10.0 (7.0–14.0)	6.0 (4.0–10.0)	<0.001***
		3	304	1.0 (0.0–3.0)	1.0 (0.0–3.0)	0.018*	363	10.0 (7.0–14.0)	6.0 (3.0–9.0)	<0.001***
		6	210	1.0 (0.0–3.0)	1.0 (0.0–3.0)	0.041*	204	9.0 (7.0–14.0)	6.0 (4.0–8.8)	<0.001***
	SQS	1	424	5.0 (3.0–7.0)	6.0 (5.0–8.0)	<0.001***	553	3.0 (2.0–5.0)	5.0 (3.0–7.0)	<0.001***
		3	297	5.0 (3.0–7.0)	7.0 (5.0–8.0)	<0.001***	348	3.0 (2.0–5.0)	5.0 (3.0–7.0)	<0.001***
		6	204	6.0 (4.0–8.0)	7.0 (5.0–8.0)	<0.001***	194	3.0 (2.0–6.0)	5.0 (3.0–7.0)	<0.001***
	PGIC	1	419	*n/a*	6.0 (5.0–6.0)	*n/a*	540	n/a	5.0 (4.0–6.0)	*n/a*
		3	294	*n/a*	6.0 (5.0–6.0)	*n/a*	344	n/a	6.0 (5.0–6.0)	*n/a*
		6	206	*n/a*	6.0 (5.0–7.0)	*n/a*	199	n/a	6.0 (5.0–6.0)	*n/a*

*Abbreviations: BPI = Brief Pain Inventory Short Form, GAD-7 = Generalized Anxiety Disorder-7, HRQoL-Health-Related Quality of Life, IQR = interquartile range, n = Number of Participants, PGIC = Patient Global Impression of Change Score, PROM = Patient-Reported Outcome Measure, SF-MPQ-2 = Short-Form McGill Pain Questionnaire-2, n/a = Not Applicable, SQS = Sleep Quality Scale, VAS = Visual Analogue Scale. Missing Data: Participants in the no anxiety (n = 99) and anxiety (n = 137) cohort did complete any follow-up PROMS. Significant differences are denoted by asterixis (*p < 0.050, **p < 0.010, ***p < 0.001).*

mild anxiety cohort. Inter-anxiety severity differences were also observed (*Appendix H*).

3.4. Opioid Medications

Figure 1 displays daily OMEs for patients concomitantly prescribed opioids at baseline and final follow-up for both cohorts. The no anxiety cohort OME decreased from 24.0 (IQR:10.0–52.5) mg/day to 20.0 (IQR:6.9–40.0) mg/day (p < 0.001). The median anxiety cohort OME remained there same, however was a statistically significant reduction in OMEs across the cohort, as reflected in a lower IQR [baseline: 24.0 (IQR:12.0–40.0) mg/day; final follow-up : 24.0(IQR:10.0–40.0) mg/day; p = 0.007]. However, the median change in OME for both cohorts was 0.0 (IQR:0.0–0.0) mg/day (p = 0.090). For analysis according to anxiety severity, see *Appendix I*.

Table 5. Median change in patient-reported outcome measures from baseline and follow-up of study participants (n = 1018).

Patient Reported Outcome Measure		Follow-Up (month)	No Anxiety		Anxiety		p-value
			n	Change Between Baseline to Follow-up *Median (IQR)*	n	Change Between Baseline to Follow-up *Median (IQR)*	
PAIN-SPECIFIC PROMs	BPI Pain Interference	1	413	-0.7 (-2.0-0.4)	542	-1.0 (-2.2-0.1)	0.015*
		3	292	-0.9 (-2.4-0.1)	343	-1.3 (-2.7- -0.1)	0.061
		6	197	-0.7 (-2.0-0.6)	186	-1.3 (-2.6-0.0)	0.010*
	BPI Pain Severity	1	413	-0.5 (-1.5-0.3)	542	-0.5 (-1.5-0.3)	0.176
		3	292	-0.5 (-1.5-0.3)	343	-0.8 (-2.0-0.0)	0.033*
		6	197	-0.5 (-2.0-0.3)	186	-0.8 (-1.8-0.0)	0.455
	SF-MPQ-2 Affective Pain	1	403	-0.5 (-1.8-0.3)	525	-0.8 (-2.3-0.3)	0.055
		3	282	-0.5 (-1.5-0.3)	337	-1.0 (-2.6-0.3)	<0.001***
		6	189	-0.3 (-2.0-0.5)	183	-1.3 (-3.0- -0.3)	<0.001***
	SF-MPQ-2 Continuous Pain	1	403	-0.8 (-1.7-0.3)	525	-0.7 (-1.8-0.3)	0.845
		3	282	-0.8 (-1.8-0.2)	337	-0.8 (-2.3-0.2)	0.255
		6	189	-0.8 (-2.3-0.3)	183	-1.2 (-2.3- -0.3)	0.046*
	SF-MPQ-2 Intermittent Pain	1	403	-0.5 (-1.7-0.5)	525	-0.7 (-2.0-0.3)	0.029*
		3	282	-0.7 (-1.9-0.2)	337	-0.8 (-2.3-0.2)	0.299
		6	189	-0.7 (-1.8-0.3)	183	-1.0 (-2.5-0.0)	0.029*
	SF-MPQ-2 Neuropathic Pain	1	403	-0.3 (-1.0-0.3)	525	-0.3 (-1.3-0.3)	0.210
		3	282	-0.3 (-1.2-0.2)	337	-0.5 (-1.5-0.2)	0.293
		6	189	-0.3 (-1.3-0.2)	183	-0.7 (-1.8-0.2)	0.068
	SF-MPQ-2 Overall Pain Score	1	403	-0.5 (-1.3-0.2)	525	-0.7 (-1.6-0.2)	0.060
		3	282	-0.6 (-1.4-0.0)	337	-0.9 (-2.0-0.1)	0.041*
		6	189	-0.7 (-1.6-0.2)	183	-1.2 (-2.3- -0.3)	0.001**
	VAS-Pain	1	409	-1.0 (-2.0-0.0)	530	-1.0 (-2.0-0.0)	0.923
		3	286	-1.0 (-2.0-0.0)	340	-1.0 (-2.0-0.0)	0.741
		6	191	-1.0 (-2.0-0.0)	184	-1.0 (-3.0-0.0)	0.067
	EQ-5D-5L Pain and Discomfort	1	433	0.0 (-1.0-0.0)	564	-1.0 (-1.0-0.0)	<0.001***
		3	303	0.0 (-1.0-0.0)	358	-1.0 (-1.0-0.0)	0.003**
		6	208	0.0 (-1.0-0.0)	201	-1.0 (-1.0-0.0)	0.008**
	EQ-5D-5L Anxiety and Depression	1	433	0.0 (0.0-0.0)	564	0.0 (-1.0-0.0)	<0.001***
		3	303	0.0 (0.0-0.0)	358	0.0 (-1.0-0.0)	<0.001***
		6	208	0.0 (0.0-0.0)	201	0.0 (-1.0-0.0)	<0.001***
	EQ-5D-5L Mobility	1	433	0.0 (-1.0-0.0)	564	0.0 (-1.0-0.0)	0.056
		3	303	0.0 (-1.0-0.0)	358	0.0 (-1.0-0.0)	0.336
		6	208	0.0 (-1.0-0.0)	201	0.0 (-1.0-0.0)	0.048*

(*Continued*)

Table 5. (Continued).

HRQoL-Related PROMs	EQ-5D-5L Self-Care	1	433	0.0 (0.0-0.0)	564	0.0 (0.0-0.0)	0.209
		3	303	0.0 (0.0-0.0)	358	0.0 (-1.0-0.0)	0.307
		6	208	0.0 (0.0-0.0)	201	0.0 (-1.0-0.0)	0.027*
	EQ-5D-5L Usual Activities	1	433	0.0 (-1.0-0.0)	564	0.0 (-1.0-0.0)	0.004**
		3	303	0.0 (-1.0-0.0)	358	0.0 (-1.0-0.0)	0.034*
		6	208	0.0 (-1.0-0.0)	201	-1.0 (-1.0-0.0)	<0.001***
	EQ-5D-5L Index Value	1	433	0.0 (0.0-0.2)	564	0.2 (0.0-0.3)	<0.001***
		3	303	0.0 (0.0-0.2)	358	0.2 (0.0-0.3)	<0.001***
		6	208	0.0 (0.0-0.2)	201	0.1 (0.0-0.4)	<0.001***
	GAD-7	1	438	0.0 (-1.0-1.0)	569	-3.0 (-6.0-0.0)	<0.001***
		3	304	0.0 (-1.0-1.0)	363	-4.0 (-7.0- -1.0)	<0.001***
		6	210	0.0 (-1.0-1.0)	204	-3.0 (-7.0- -0.3)	<0.001***
	SQS	1	424	1.0 (-1.0-3.0)	553	1.0 (0.0-3.0)	0.002**
		3	297	1.0 (0.0-3.0)	348	1.0 (0.0-3.0)	0.023*
		6	204	0.0 (-1.0-2.0)	194	1.0 (0.0-3.0)	0.002**

*Abbreviations: BPI = Brief Pain Inventory Short Form, GAD-7 = Generalized Anxiety Disorder-7, HRQoL-Health-Related Quality of Life, IQR = interquartile range, n = Number of Participants, PGIC = Patient Global Impression of Change Score, PROM = Patient-Reported Outcome Measure, SF-MPQ-2 = Short-Form McGill Pain Questionnaire-2, n/a = Not Applicable, SQS = Sleep Quality Scale, VAS = Visual Analogue Scale. Missing Data: Participants in the no anxiety (n = 99) and anxiety (n = 137) cohort did complete any follow-up PROMS. Significant differences are denoted by asterixis (*p < 0.050, **p < 0.010, ***p < 0.001). For ease of interpretation, a color key is used for the 3 outcomes observed: a statistically significantly greater improvement in the anxiety cohort, a statistically insignificantly greater improvement in the anxiety cohort or a statistically insignificantly greater improvement in the no anxiety cohort was observed.*

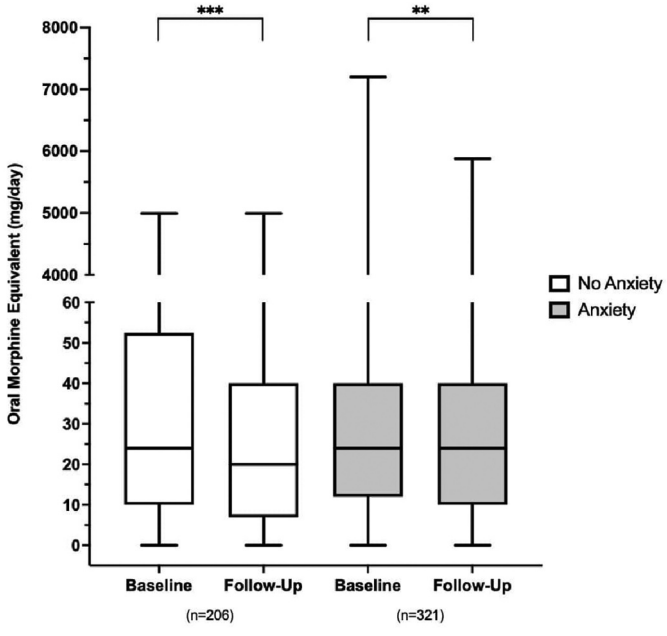

Figure 1. Paired oral morphine equivalent (OME) doses (mg/day) at baseline and the end of follow-up for study participants (n = 527). An axis break was introduced between the 75th percentile and the maximum values (between 60.0–4000.0 mg/day) to enable optimal visualization of the box plot. Missing data: Opioid prescription dose was unavailable in the no anxiety cohort (n = 53) and the anxiety cohort (n = 71) due to incomplete data inputting or the 'pro re nata' (PRN) nature of the prescription. Significant differences are denoted by asterixis (*p < 0.050, **p < 0.010, ***p < 0.001).

3.5. Adverse Events

91 (16.8%) participants in the no anxiety and 138 (19.4%) participants in the anxiety cohort experienced at least 1 AE (p = 0.229). The most common AEs in the no anxiety cohort were fatigue (n = 78; 14.4%) and somnolence (n = 61; 11.4%) opposed to fatigue (n = 117; 16.5%) and dry mouth (n = 104; 14.6%) in the anxiety cohort. For specific AEs reported, according to anxiety severity, see *Appendix J*.

Figure 2 displays the frequency of AEs in both cohorts, separated into AE severity, throughout the study. Total AEs experienced was higher in the anxiety (n = 1473, 207.2%) cohort compared to the anxiety (n = 879; 161.9%) cohort.

3.6. Univariate and multivariate analysis

The univariate analysis for variables analyzed for their effect on BPI pain interference found no significance, but the multivariate analysis found those with anxiety (OR = 2.016, 95% CI = 1.203–3.379; p = 0.008) to have an increased odds of observing an improvement. The univariate and multivariate analysis for BPI pain severity found BMI ≤20 (OR = 0.362; 95%CI = 0.154–0.849; p = 0.020 and OR = 0.298; 95% CI = 0.115–0.775; p = 0.013 respectively) to reduce the likelihood of improvement.

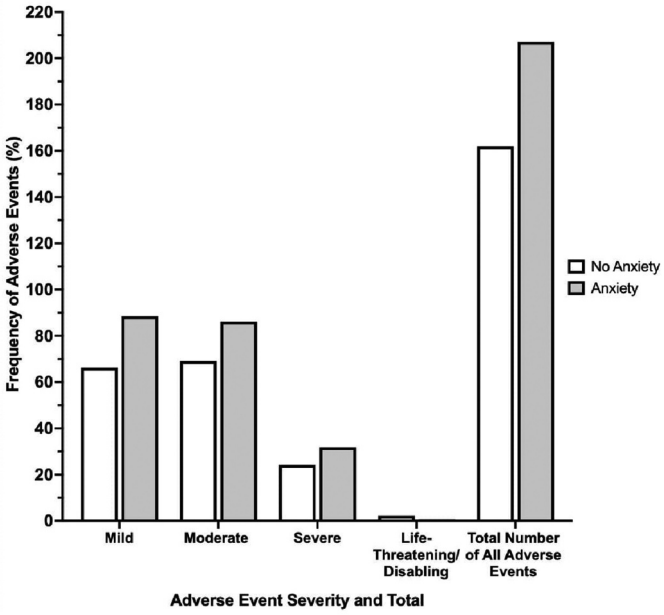

Figure 2. Adverse event frequency separated into severity for study participants (n = 1254) from baseline to 6 months. The total number of all adverse events is also displayed.

The univariate analysis for variables analyzed for their effect on AE likelihood found female gender (OR = 2.325; 95% CI = 1.731–3.125; p < 0.001) was associated with increased AE likelihood. Current cannabis consumption at baseline (OR = 0.376; 95%CI = 0.274–0.516; p < 0.001), vaporized flower only administration of CBMPs (OR = 0.556; 95%CI = 0.346–0.892; p = 0.015) and both sublingual/oral and vaporized flower administration of CBMPs (OR = 0.694; 95%CI = 0.503–0.956; p = 0.026) were associated with reduced AE likelihood. On multivariate analysis female gender (OR = 2.075; 95% CI = 1.455–2.960; p < 0.001) was associated with increased AE likelihood whilst current cannabis consumption at baseline (OR = 0.406; 95%CI = 0.261–0.631; p < 0.001) was associated with decreased AE odds.

For full analyses, see *Appendix K-P*.

4. Discussion

4.1. Summary

This UKMCR cohort study of CP patients with and without anxiety demonstrated improvements in all pain-specific PROMs in both cohorts and HRQoL PROMs in the anxiety cohort and most in the no anxiety cohort at 1, 3, and 6 months. The anxiety cohort achieved greater improvements in anxiety, sleep, and HRQoL at 1, 3, and 6 months compared to the no anxiety cohort.

However, the results across all pain-specific PROMs were inconsistent, as although the anxiety cohort generally achieved greater pain reductions, these were not always statistically significant. Both cohorts achieved significant reductions in opioid consumption, but no difference was observed in the magnitude of reduction between cohorts. There was no difference in the proportion of patients in each cohort experiencing an AE.

4.2. Patient-reported outcome measures

Initiation of CBMPs was associated with reductions in pain-specific PROMs at all timepoints in both cohorts. This is corroborated by two prospective open-label observational studies by Safakish et al [21]. and Haroutounian et al [22]., in which BPI pain severity and interference were reduced following 6-months of CBMPs. However, the reductions were generally greater in both studies than the present analyses. Possible explanations include the lower CBMP dosages used and larger sample size in this study, as well as differences in baseline demographics and pain parameters [21,22]. Conversely, Campbell et al [30]. concluded that no relationship existed between initiating treatment with cannabis and pain severity or interference. Importantly, illicit cannabis was utilized, thus cannabinoid and non-cannabinoid compound contents and dosing were unpredictable between patients and for each patient. Moreover, illicit cannabis can contain contaminants that can be deleterious to health [94–96], potentially contributing to the lack of observed improvements [21,30]. This contrasts the GMP manufactured CBMP prescriptions used in this study, in which consistency was ensured [75].

When comparing both cohorts, the anxiety cohort mostly achieved greater reductions in pain-specific PROMs, but statistical significance was not always reached. Additionally, multivariate analysis of BPI pain interference revealed anxiety to increase the odds of improvement independently of other considered variables. Together this indicates CP patients with co-morbid anxiety may achieve better pain-specific outcomes, but the magnitude and reliability of this finding is uncertain. Potential reasons for the anxiety cohort achieving greater overall pain improvements include concomitant improvements in central sensitization [47] and pain catastrophizing [53], which are more prevalent in those with anxiety cohorts [42–46,49,53–55,57–59].

There were associated reductions in anxiety, as assessed by the GAD-7, in the anxiety cohort. However, anxiety marginally increased in the no anxiety cohort. The reduction in anxiety in the anxiety cohort is consistent with the clinical studies also showing reductions in anxiety following CBMP treatment, however these limited studies focused on only social anxiety and used different PROMs compared to this study, so direct comparison is difficult [35,37]. Moreover, it may be expected for anxiety to have decreased for over 50% of the participants who were illicit cannabis users through accessing legal CBMP treatment, due to a reduction in the potential stress and stigma analogous with illicit drug use [21,97,98].

Potential explanations for the unexpected anxiety increase in the no anxiety cohort may include how participants were divided into their respective cohorts. This was based solely on baseline GAD-7 scores, which only considers anxiety status over the last two weeks [69,70], as opposed to a clinical diagnosis which requires anxiety symptoms to be present for at least six months [99]. Hence, it cannot be certain the anxiety cohort represented those with trait anxiety (a more stable personality feature) and not state anxiety (a transient reaction to adverse life events) only, or that the no anxiety cohort did not contain participants with trait anxiety whose anxiety level was low at the time of baseline GAD-7 collection [100].

Moreover, those with and without anxiety at baseline would have been subject to scale attenuation effects due to constraints of the range of GAD-7 scores. Furthermore, despite the median dosages of CBD and THC being identical for both cohorts, the THC IQR was higher, and CBD IQR was lower in the no anxiety cohort, so it is possible the anxiogenic effects of THC were increased whilst the protective and anxiolytic effects CBD were decreased [16,101–103]. Furthermore, the median GAD-7 value and IQR remained unchanged at each follow-up, so the clinical relevance of this likely to be small, if not negligible. Importantly, it must be acknowledged that only four adverse events of 'anxiety' were recorded in the no anxiety cohort (n = 543), of which two were mild, one moderate, and one severe in severity. Nevertheless, further robust research is required.

The HRQoL-related PROM improvements in the anxiety cohort were consistently greater than the no anxiety cohort, with the exception of the EQ-5D-5L mobility and self-care scores and the pain-specific PROMs, which yielded less conclusive results. Therefore, it is possible that CBMPs predominantly improved HRQoL through associated changes in psychological domains rather than direct anti-nociceptive effects. Hence implying the anxiety cohorts' greater improvements are more related to CBMPs' psychoactive properties as opposed to functional improvements [74]. Interestingly, a pre-clinical study found that THC may not significantly impact the sensory aspect of pain but instead the affective perception of pain [48]. Furthermore, the PROMs subgroup analysis according to anxiety severity revealed individuals with more severe anxiety have larger associated PROM improvements compared to the no anxiety cohort. This is corroborated by a retrospective study that only observed improvements in those with moderate-to-severe pain or anxiety symptoms, potentially due to the larger margin for symptom improvement [104].

4.3. Adverse events and opioid consumption

Opioid consumption reduced for both cohorts, consistent with existing literature [21,22,105–108], but the reductions were not clinically significant [109]. There was no difference between the proportion of patients in each cohort experiencing an adverse event in the no anxiety (16.8%) and anxiety (19.4%) cohorts, and in both cohorts over 80% of AEs were mild or moderate in severity. Similarly, the COMPASS study found 13.0% of participants prescribed CBMPs experienced an AE, and most were also mild or moderate [19]. The larger proportion observed in this study's anxiety cohort could be due to increased health anxiety, linked to generalized anxiety [110,111], and hence greater AE perception and self-reporting [112]. Univariate and multivariate analysis of AE likelihood revealed that cannabis use at baseline was associated with reduced AE likelihood, supporting existing studies that suggest tolerance to cannabinoids develops with long-term use, an important consideration when starting therapy [113].

4.4. Limitations and the future

The inherent limitation of this study is the inability to determine causality due to its observational design [114]; thus, it cannot be certain that observed improvements or AEs were due to CBMPs and not another confounding factor. To combat this, multivariate analyses were conducted; albeit not all factors were accounted for, including concomitant non-opioid analgesia or non-pharmacological therapy use. Furthermore, there was no placebo control, thus the true magnitude of CBMPs' effects cannot be ascertained due to potential placebo effect. The open-label design further compounds this as unblinded self-reporting participants often exaggerate perceived benefits [115].

There were various sources of bias, including selection bias, as all patients were from the same private clinic, limiting inclusion to those who can afford treatment. To gain insight into participants' socioeconomic status, occupation status data was collected, which revealed high unemployment (37.4% and 51.3%), suggesting a bias toward the wealthy was not definite. Although a more comprehensive index of present socioeconomic status would better evaluate this. Over 50% of participants were current cannabis users prior to enrollment in the UKMCR who may be more likely to report positive outcomes due to expectancy of effect. Moreover, there is an additional selection bias as these individuals are more likely to have experienced improvements in their symptoms whilst consuming cannabis purchased illicitly in the past, whilst those who have consumed cannabis previously and found it to have no effect on their symptoms would be less likely to explore treatment with CBMPs. Conversely, participants with previous illicit consumption may have developed tolerance to the effects of CBD and THC [116], reducing the magnitude of changes in HRQoL experienced when initiating CBMPs. PROMs are subject to recall bias, further affecting the applicability of the results. In comparison, clinician outcome measures provide more objective measurement of disease [117]. PROMs, do, however, benefit from being blinded to clinicians, therefore reducing any additional expectancy bias. Moreover, as they are less resource intensive to collect, they may have resulted in improved follow up, compared to a comparative dataset where PROMs were substituted for clinician assessment [118]. Considerable loss to follow-up, however, was observed, and the reasons for this were not collected, so attrition bias may have played a role, and it cannot be certain that the ongoing improvements at up to 6 months was due to CBMPs and not the reduction in sample size.

Future studies could stratify outcomes based on chronic pain etiology and severity, anxiety disorder type and cannabis formulation and administration route. Despite the present study being longer than most CBMP studies, longer studies are still required to evaluate longer term outcomes and safety. Additional pre-clinical studies are necessary to reveal the exact underlying mechanism behind the greater improvements observed in CP patients with co-morbid anxiety. However, standardized high-quality randomized control trials are ultimately required [119].

5. Conclusion

A potential association between initiation of CBMPs and improvements in pain and HRQoL, as well as reductions in opioid consumption and an acceptable AE profile in both cohorts was found, complimenting previous UKMCR studies. Moreover, CP patients with co-morbid anxiety may achieve better HRQoL outcomes and potentially pain outcomes due to CBMPs' peripheral and central effects.

Due to the pertinent limitations of this study, namely its observational nature, its results should be interpreted with caution. More research is ultimately required to determine that the changes observed were not secondary to confounding factors beyond the control of the study design. As this is the first study assessing the effects of CBMPs in patients with co-morbid anxiety, hopefully it will act to guide further assessment within RCTs.

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Declaration of Interest

S Erridge undertakes paid consultancy work at Sapphire Medical Clinics. C Holvey is chief clinical pharmacist at Sapphire Medical Clinics. R Coomber is a director at Sapphire Medical Clinics. The views expressed are those of the author(s) and not necessarily those of the NHS. Ross Coomber has no shareholdings in pharmaceutical companies, while A Usmani and M Sajad are pain specialists at Sapphire Medical Clinics (London). J Hoare is a consultant in gastroenterology at Sapphire Medical Clinics (London) while SA Khan is a consultant in palliative medicine at Sapphire Medical Clinics (London. MW Weatherall is also a consultant Sapphire Medical Clinics (London). JJ Rucker is a consultant psychiatrist, a director and a shareholder at Sapphire Medical Clinics (London). He is is funded by a fellowship (CS-2017-17-007) from the National Institute for Health Research (NIHR). He also leads the Psychedelic Trials Group at King's College London. King's College London receives grant funding from COMPASS Pathways PLC to undertake phase 1 and phase 2 trials with psilocybin. COMPASS Pathways PLC has paid for J Rucker to attend trial related meetings and conferences to present the results of research using psilocybin. He also has undertaken paid consultancy work for Beckley PsyTech and Clerkenwell Health. Payments for consultancy work are received and managed by King's College London and he does not benefit personally. James Rucker has no shareholdings in pharmaceutical companies. M Platt is a consultant in pain services at Sapphire Medical Clinics (London). MH Sodergren is a consultant hepatopancreatobiliary surgeon at Imperial College NHS Trust, London. He is also the Managing Director of Sapphire Medical Clinics (London) and the Chief Medical Officer of Curaleaf International. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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All authors have contributed to and approved the final manuscript. All conditions as previously stated by the ICMJE have been met.

Data Availability Statement

Data that support the findings of this study are available from the UK Medical Cannabis Registry (https://ukmedicalcannabisregistry.com/). Restrictions apply to the availability of these data. Data specifications and applications are available from the corresponding author.

Ethics Approval

In the UK, ethics approval is not required for purely registry-based studies.

Patient Consent Statement

All participants completed written, informed consent prior to enrolment in the registry.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Ellis B, Ly M, Steinberger S Versus arthritis: chronic pain in England. 2021 [cited 2022 May 5]; Available from: www.versusarthritis.org.
2. Hylands-White N, Duarte RV, Raphael JH. An overview of treatment approaches for chronic pain management. Rheumatol Int. Internet]. 2017 [cited 2022 May 8];37:29–42. Available from;:.:https://link.springer.com/article/10.1007/s00296-016-3481-8
3. Donvito G, Nass SR, Wilkerson JL, et al. The endogenous cannabinoid system: a budding source of targets for treating inflammatory and neuropathic pain. Internet]. 2017 [cited 2022 May 12];43:52–79. Available from. Neuropsychopharmacology. 2018;:.https://www.nature.com/articles/npp2017204
4. Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: Δ9-tetrahydrocannabinol, cannabidiol and Δ9-tetrahydrocannabivarin. Br J Pharmacol. Internet]. 2008 [cited 2022 May 12];153:199–215. Available from;:.:https://onlinelibrary.wiley.com/doi/full/10.1038/sj.bjp.0707442
5. Mlost J, Bryk M, Starowicz K. Cannabidiol for pain treatment: focus on pharmacology and mechanism of action. Int J Mol Sci Internet]. 2020 [cited 2022 May 12];21:1–22. Available from https://pubmed.ncbi.nlm.nih.gov/33238607/
6. Mechoulam R, Parker LA The endocannabinoid system and the brain. 2012 [cited 2022 May 11]; Available from: www.annualreviews.org.
7. Price TJ, Helesic G, Parghi D, et al. The neuronal distribution of cannabinoid receptor type 1 in the trigeminal ganglion of the rat. Neuroscience. 2003;120:155–162.

8. Hill KP, Palastro MD, Johnson B, et al. Cannabis and pain: a clinical review. Cannabis Cannabinoid Res Internet]. 2017 [cited 2022 May 12];2:96–104. Available from https://www.liebertpub.com/doi/full/10.1089/can.2017.0017
9. Vučkovic S, Srebro D, Vujovic KS, et al. Cannabinoids and pain: new insights from old molecules. Front Pharmacol. 2018;9:1259.
10. Cristino L, Bisogno T, Di Marzo V. Cannabinoids and the expanded endocannabinoid system in neurological disorders. Nat Rev Neurol. Internet] [cited 2022 May 11];16:9–29. Available from;2019 https://www.nature.com/articles/s41582-019-0284-z
11. Brodermann H, Pain M. pleasure and placebo: the cannabinoids in reward processing and the perception of pain. Ment Health Addict Res. 2016;1. DOI:10.15761/MHAR.1000115
12. Russo EB, THC T. potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. Br J Pharmacol. Internet]. 2011 [cited 2022 May 12];163:1344–1364. Available from https://onlinelibrary.wiley.com/doi/full/10.1111/j.1476-5381.2011.01238.x
13. Laprairie RB, Bagher AM, Kelly MEM, et al. Cannabidiol is a negative allosteric modulator of the cannabinoid CB1 receptor. Br J Pharmacol Internet]. 2015 [cited 2022 May 12];172:4790–4805. Available from.https://onlinelibrary.wiley.com/doi/full/10.1111/bph.13250
14. de Petrocellis L, Ligresti A, Moriello AS, et al. Effects of cannabinoids and cannabinoid-enriched Cannabis extracts on TRP channels and endocannabinoid metabolic enzymes. Br J Pharmacol Internet]. 2011 [cited 2022 May 12];163:1479–1494. Available from. https://onlinelibrary.wiley.com/doi/full/10.1111/j.1476-5381.2010.01166.x
15. Aurora. Cannabis Compendium. 2020 [cited 2022 May 11]; Available from: https://www.cannaconnect.ca/wp-content/uploads/2020/10/Aurora-Cannabis-Medical-Compendium.pdf.
16. Finn K. Cannabis in medicine: an evidence-based approach.2020. Springer Nature. [cited 2022 May 11].
17. Anand U, Jones B, Korchev Y, et al. CBD effects on TRPV1 signaling pathways in cultured DRG neurons. J Pain Res Internet]. 2020 [cited 2022 May 23];13:2269–2278. Available from. https://www.dovepress.com/cbd-effects-on-trpv1-signaling-pathways-in-cultured-drg-neurons-peer-reviewed-fulltext-article-JPR
18. Romero-Sandoval EA, Fincham JE, Kolano AL, et al. Cannabis for chronic pain: challenges and considerations. Pharmacother J Human Pharmacol Drug Ther Internet]. 2018 [cited 2022 May 20];38:651–662. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/phar.2115
19. Ware MA, Wang T, Shapiro S, et al. Cannabis for the management of pain: assessment of safety study (COMPASS). J Pain Internet]. 2015 [cited 2022 May 20];16:1233–1242. Available from. https://pubmed.ncbi.nlm.nih.gov/26385201/
20. Überall MA. A review of scientific evidence for THC:CBD oromucosal spray (nabiximols) in the management of chronic pain. J Pain Res Internet]. 2020 [cited 2022 May 20];13:399.Available from:. /pmc/articles/PMC7027889/
21. Safakish R, Ko G, Salimpour V, et al. Medical cannabis for the management of pain and quality of life in chronic pain patients: a prospective observational study. Pain Med Internet]. 2020 [cited 2022 May 20];21:3073–3086. Available from https://pubmed.ncbi.nlm.nih.gov/32556203/
22. Haroutounian S, Ratz Y, Ginosar Y, et al. The effect of medicinal cannabis on pain and quality-of-life outcomes in chronic pain: a prospective open-label study. Clin J Pain Internet]. 2016 [cited 2022 May 20];32:1036–1043. Available from https://pubmed.ncbi.nlm.nih.gov/26889611/
23. Greis A, Larsen E, Liu C, et al. Perceived efficacy, reduced prescription drug use, and minimal side effects of cannabis in patients with chronic orthopedic pain. Cannabis Cannabinoid Res Internet]. 2021 [cited 2021 May 20]; Available from. 7:865–875 . https://pubmed.ncbi.nlm.nih.gov/34767730/
24. Ueberall MA, Essner U, Mueller-Schwefe GHH. Effectiveness and tolerability of THC:CBD oromucosal spray as add-on measure in patients with severe chronic pain: analysis of 12-week open-label real-world data provided by the German pain e-registry. J Pain Res Internet]. 2019 [cited 2022 May 22];12:1577–1604. Available from. https://www.dovepress.com/effectiveness-and-tolerability-of-thccbd-oromucosal-spray-as-add-on-me-peer-reviewed-fulltext-article-JPR
25. Abelev S, Warne LN, Benson M, et al. Medicinal cannabis for the treatment of chronic refractory pain: an investigation of the adverse event profile and health-related quality of life impact of an oral formulation. Preclinical Sci Clin Studies-Res Article Med Cannabis Cannabinoids. Internet]. 2022 [cited. 2022. 5: 20–31. Available from. www.karger.com/mca
26. Gruber SA, Smith RT, Dahlgren MK, et al. No pain, all gain? Interim analyses from a longitudinal, observational study examining the impact of medical cannabis treatment on chronic pain and related symptoms. Exp Clin Psychopharmacol. 2021;29:147–156.
27. Peterson AM, Le C, Dautrich T. Measuring the change in health-related quality of life in patients using marijuana for pain relief. Med Cannabis Cannabinoids Internet]. 2021 [cited 2022 May 24];4:114–120. Available from. https://www.karger.com/Article/FullText/517857
28. Wang L, Hong PJ, May C, et al. Medical cannabis or cannabinoids for chronic non-cancer and cancer related pain: a systematic review and meta-analysis of randomised clinical trials. BMJ. Internet]. 2021 [cited 2022 May 20];374. Available from:. https://www.bmj.com/content/374/bmj.n1034.

•• **A systematic review and meta-analysis on chronic pain outcomes in those prescribed medical cannabis or cannabinoids.**

29. Mücke M, Phillips T, Radbruch L, et al. Cannabis-based medicines for chronic neuropathic pain in adults. Cochrane Database Syst Rev [Internet]. 2018 [cited 2022 May 20];3. Available from: https://pubmed.ncbi.nlm.nih.gov/29513392/.
30. Campbell G, Hall WD, Peacock A, et al. Effect of cannabis use in people with chronic non-cancer pain prescribed opioids: findings from a 4-year prospective cohort study. Lancet Public Health Internet]. 2018 [cited 2022 May 20];3:e341–e350. Available from. http://www.thelancet.com/article/S2468266718301105/fulltext
31. Häuser W, Petzke F, Fitzcharles MA. Efficacy, tolerability and safety of cannabis-based medicines for chronic pain management – an overview of systematic reviews. European J Pain (United Kingdom). 2018;22:455–470.
32. Black N, Stockings E, Campbell G, et al. Cannabinoids for the treatment of mental disorders and symptoms of mental disorders: a systematic review and meta-analysis. Lancet Psychiatry Internet]. 2019 [cited 2022 May 24];6:995–1010. Available from.http://www.thelancet.com/article/S2215036619304018/fulltext
33. Asmundson GJG, Psych RD, Mcmillan KA, et al. Understanding and managing clinically significant pain in patients with an anxiety disorder. Focus [Internet]. 2011 [cited 2022 May 19];9:264–272. Available from. https://focus.psychiatryonline.org/doi/full/10.1176/foc.9.3.foc264.

•• **A review of the management chronic pain and its complex interplay with co-morbid anxiety**

34. Demyttenaere K, Bruffaerts R, Lee S, et al. Mental disorders among persons with chronic back or neck pain: results from the world mental health surveys. Pain Internet]. 2007 [cited 2022 May 19];129:332–342. Available from.https://journals.lww.com/pain/Fulltext/2007/06000/Mental_disorders_among_persons_with_chronic_back.13.aspx
35. Masataka N. Anxiolytic effects of repeated cannabidiol treatment in teenagers with social anxiety disorders. Front Psychol. 2019;10:2466.
36. Martin EL, Strickland JC, Schlienz NJ, et al. Antidepressant and ANXIOLYTIC EFFECTS OF MEDICINAL CANNABIS USE IN AN OBSERVATIONAL TRIAL. Front Psychiatry. 2021;12:1554.
37. Crippa JAS, Nogueira Derenusson G, Borduqui Ferrari T, et al. Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: a preliminary report. J Psychopharmacol Internet]. 2011 [cited 2022 May 20];25:121–130. Available from. https://journals.sagepub.com/doi/10.1177/0269881110379283

38. Meints SM, Edwards RR. Evaluating psychosocial contributions to chronic pain outcomes. Prog Neuropsychopharmacol Biol Psychiatry. 2018;87:168–182.
39. Edwards RR, Dworkin RH, Sullivan MD, et al. The role of psychosocial processes in the development and maintenance of chronic pain. J Pain. 2016;17:T70–T92.
40. de Heer EW, Gerrits MMJG, Beekman ATF, et al. The association of depression and anxiety with pain: a study from NESDA. PLoS One Internet]. 2014 [cited 2022 May 20];9:e106907. Available from. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0106907
41. Teh CF, Morone NE, Karp JF, et al. Pain interference impacts response to treatment for anxiety disorders. Depress Anxiety Internet]. 2009 [cited 2022 May 20];26:222.Available from:. /pmc/articles/PMC2836014/
42. Carter LE, McNeil DW, Vowles KE, et al. Effects of emotion on pain reports, tolerance and physiology. Pain Res Manag Internet]. 2002 [cited 2022 May 19];7:21–30. Available from. https://pubmed.ncbi.nlm.nih.gov/16231064/
43. Clark JR, Yeowell G, Goodwin PC. Trait anxiety and sensory processing profile characteristics in patients with non-specific chronic low back pain and central sensitisation - A pilot observational study. J Bodyw Mov Ther. 2018;22:909–916.
44. Engel-Yeger B, Dunn W. The relationship between sensory processing difficulties and anxiety level of healthy adults. British Journal of Occupational Therapy [Internet]. 2011 [cited. 2022;74:.210–216.
45. Asmundson GJG, Katz J. Understanding the co-occurrence of anxiety disorders and chronic pain: state-of-the-art. Depress Anxiety. Internet]. 2009 [cited 2022 May 20];26:888–901. Available from;:.: https://onlinelibrary.wiley.com/doi/full/10.1002/da.20600
46. Burston JJ, Valdes AM, Woodhams SG, et al. The impact of anxiety on chronic musculoskeletal pain and the role of astrocyte activation. Pain Internet]. 2019 [cited 2022 May 20];160:658–669. Available from. https://journals.lww.com/pain/Fulltext/2019/03000/The_impact_of_anxiety_on_chronic_musculoskeletal.13.aspx
47. Nijs J, George SZ, Clauw DJ, et al. Central sensitisation in chronic pain conditions: latest discoveries and their potential for precision medicine. Lancet Rheumatol Internet]. 2021 [cited 2022 May 20];3:e383–e392. Available from.;: . http://www.thelancet.com/article/S2665991321000321/fulltext
48. Lee MC, Ploner M, Wiech K, et al. Amygdala activity contributes to the dissociative effect of cannabis on pain perception. Pain. 2013;154:124–134.
49. Burston JJ, Sagar DR, Shao P, et al. Cannabinoid CB2 receptors regulate central sensitization and pain responses associated with osteoarthritis of the knee joint. PLoS One Internet]. 2013 [cited 2022 May 20];8:e80440. Available from. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0080440
50. Abraham AD, Leung EJY, Wong BA, et al. Orally consumed cannabinoids provide long-lasting relief of allodynia in a mouse model of chronic neuropathic pain. Neuropsychopharmacology Internet] [cited 2022 May 20];45:1105–1114. Available from.;2019 https://www.nature.com/articles/s41386-019-0585-3
51. Philpott HT, O'Brien M, McDougall JJ. Attenuation of early phase inflammation by cannabidiol prevents pain and nerve damage in rat osteoarthritis. Pain Internet]. 2017 [cited 2022 May 20];158:2442. Available from:. /pmc/articles/PMC5690292/
52. van de Donk T, Niesters M, Kowal MA, et al. An experimental randomized study on the analgesic effects of pharmaceutical-grade cannabis in chronic pain patients with fibromyalgia. Pain Internet]. 2019 [cited 2022 May 24];160:860–869. Available from. https://pubmed.ncbi.nlm.nih.gov/30585986/
53. Quartana PJ, Campbell CM, Edwards RR. Pain catastrophizing: a critical review. Expert Rev Neurother Internet]. 2009 [cited 2022 May 20];9:745.Available from:. ;:. /pmc/articles/PMC2696024/
54. Drahovzal DN, Stewart SH, Sullivan MJL. Tendency to catastrophize somatic sensations: pain catastrophizing and anxiety sensitivity in predicting headache. Cognitive Behaviour Therapy [Internet]. 2006 [cited 2022 May 20];35:226–235. Available from. https://www.tandfonline.com/doi/abs/10.1080/16506070600898397
55. Tran ST, Jastrowski Mano KE, Hainsworth KR, et al. Distinct influences of anxiety and pain catastrophizing on functional outcomes in children and adolescents with chronic pain. J Pediatr Psychol Internet]. 2015 [cited 2022 May 20];40:744–755. Available from. https://academic.oup.com/jpepsy/article/40/8/744/929254
56. Burns LC, Ritvo SE, Ferguson MK, et al. Pain catastrophizing as a risk factor for chronic pain after total knee arthroplasty: a systematic review. J Pain Res Internet]. 2015 [cited 2022 May 20];8:21–32. Available from. https://www.dovepress.com/pain-catastrophizing-as-a-risk-factor-for-chronic-pain-after-total-kne-peer-reviewed-fulltext-article-JPR
57. Vasey MW, Borkovec TD. A catastrophizing assessment of worrisome thoughts. Cognitive Ther Res. Internet] [cited 2022 May 20];16:505–520. Available from;1992 https://link.springer.com/article/10.1007/BF01175138
58. Severeijns R, Vlaeyen JWS, van den Hout MA, et al. Pain catastrophizing predicts pain intensity, disability, and psychological distress independent of the level of physical impairment. Clin J Pain Internet]. 2001 [cited 2022 May 20];17:165–172. Available from. https://pubmed.ncbi.nlm.nih.gov/11444718/
59. Slawek DE, Syed M, Cunningham CO, et al. Pain catastrophizing and mental health phenotypes in adults with refractory chronic pain: a latent class analysis. J Psychiatr Res. 2022;145:102–110.
60. Reason and emotion in psychotherapy. - PsycNET [Internet]. [cited 2022 May 20]. Available from: https://psycnet.apa.org/record/1963-01437-000.
61. Cognitive therapy of depression - google books [internet]. [cited 2022 May 20]. Available from: https://books.google.co.uk/books?hl=en&id=L09cRS0xWj0C&oi=fnd&pg=PA1&ots=FYPgaSanhk&sig=MVpgZ6IpLvN9j6yXbtwwIrkG9fg&redir_esc=y#v=onepage&q&f=false.
62. Gambi F, de Berardis D, Sepede G, et al. Cannabinoid receptors and their relationships with neuropsychiatric disorders. International Journal of Immunopathology and Pharmacology. 2016. 18, Internet] [cited 2023 Feb 4];:15–19. Available from. https://journals.sagepub.com/doi/10.1177/039463200501800103
63. Fornaro M, de Berardis D, Iasevoli F, et al. Treatment adherence towards prescribed medications in bipolar-II acute depressed patients: relationship with cyclothymic temperament and "therapeutic sensation seeking" in response towards subjective intolerance to pain. J Affect Disord Internet]. 2013 [cited 2023 Feb 6];151:596–604. Available from.;: . https://pubmed.ncbi.nlm.nih.gov/23906864/
64. NHS Health Research Authority. What approvals and decisions do I need? [Internet]. 2020 [cited 2022 May 1]. Available from: https://www.hra.nhs.uk/approvals-amendments/what-approvals-do-i-need/.
65. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. PLoS Med Internet]. 2007 [cited 2022 May 1];4:1628–1654. Available from. https://pubmed.ncbi.nlm.nih.gov/17941715/
66. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ Internet]. 2016 [cited 2023 Feb 4];355. Available from:. https://www.bmj.com/content/355/bmj.i4919
67. Harris M, Erridge S, Ergisi M, et al. UK Medical Cannabis registry: an analysis of clinical outcomes of medicinal cannabis therapy for chronic pain conditions. Expert Rev Clin Pharmacol Internet]. 2021 [cited 2022 May 20]; Available from. https://pubmed.ncbi.nlm.nih.gov/34937477/.

•• **A prior study from the UK Medical Cannabis Registry examining the outcomes in individuals prescribed cannabis-based medicinal products for chronic pain.**

68. Ergisi M, Erridge S, Harris M, et al. UK Medical Cannabis Registry: an analysis of clinical outcomes of medicinal cannabis therapy for generalized anxiety disorder. Expert Rev Clin Pharmacol Internet].

2022 [cited 2022 May 20]; Available from. ;15:487–495. https://pubmed.ncbi.nlm.nih.gov/34937473/.

•• **A prior study from the UK Medical Cannabis Registry examining the outcomes in individuals prescribed cannabis-based medicinal products for generalized anxiety disorder.**

69. Spitzer RL, Kroenke K, Williams JBW, et al. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med Internet]. 2006 [cited 2022 May 1];166:1092–1097. Available from. https://pubmed.ncbi.nlm.nih.gov/16717171/
70. Löwe B, Decker O, Müller S, et al. Validation and standardization of the generalized anxiety disorder screener (GAD-7) in the general population. Med Care Internet]. 2008 [cited 2022 May 2];46:266–274. Available from. https://pubmed.ncbi.nlm.nih.gov/18388841/
71. ISCO. ISCO - International Standard Classification of occupations [internet]. 2008 [cited 2022 May 6]. Available from: https://www.ilo.org/public/english/bureau/stat/isco/isco08/index.htm.
72. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40:373–383.
73. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol Internet]. 2011 [cited 2022 May 6];173:676–682. Available from. https://pubmed.ncbi.nlm.nih.gov/21330339/
74. Erridge S, Salazar O, Kawka M, et al. An initial analysis of the UK medical cannabis registry: outcomes analysis of first 129 patients. Neuropsychopharmacol Rep Internet]. 2021 [cited 2022 May 1];41:362–370. Available from. https://onlinelibrary.wiley.com/doi/full/10.1002/npr2.12183
75. Good manufacturing practice and good distribution practice - GOV. UK [Internet]. [cited 2022 May 2]. Available from: https://www.gov.uk/guidance/good-manufacturing-practice-and-good-distribution-practice.
76. Dansie EJ, Turk DC. Assessment of patients with chronic pain. Br J Anaesth Internet]. 2013 [cited 2022 May 2];111:19–25. Available from. http://www.bjanaesthesia.org.uk/article/S0007091217329628/fulltext
77. Outcome Measures. 2019 [cited 2022 May 2]; Available from: www.immpact.org.
78. Cleeland CS, Ryan KM. Pain assessment: global use of the brief pain inventory. Ann Acad Med Singap. 1994;23:129–138.
79. Dworkin RH, Turk DC, Revicki DA, et al. Development and initial validation of an expanded and revised version of the short-form mcgill pain questionnaire (SF-MPQ-2). Pain Internet]. 2009 [cited 2022 May 2];144:35–42. Available from. https://journals.lww.com/pain/Fulltext/2009/07000/Development_and_initial_validation_of_an_expanded.12.aspx
80. Jumbo SU, MacDermid JC, Kalu ME, et al. Measurement properties of the brief pain inventory-short form (BPI-SF) and revised short mcgill pain questionnaire version-2 (SF-MPQ-2) in pain-related musculoskeletal conditions a systematic review. Clin J Pain Internet]. 2021 [cited 2022 May 2];37:454–474. Available from. https://journals.lww.com/clinicalpain/Fulltext/2021/06000/Measurement_Properties_of_the_Brief_Pain.8.aspx
81. Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain Internet]. 2008 [cited 2022 May 6];9:105–121. Available from. https://pubmed.ncbi.nlm.nih.gov/18055266/
82. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res Internet]. 2011 [cited 2022 May 2];20:1727–1736. Available from. https://pubmed.ncbi.nlm.nih.gov/21479777/
83. van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health Internet]. 2012 [cited 2022 May 2];15:708–715. Available from. https://pubmed.ncbi.nlm.nih.gov/22867780/
84. Snyder E, Cai B, DeMuro C, et al. A new single-item sleep quality scale: results of psychometric evaluation in patients with chronic primary insomnia and depression. J Clin Sleep Med Internet]. 2018 [cited 2022 May 2];14:1849–1857. Available from. https://pubmed.ncbi.nlm.nih.gov/30373688/
85. ECDEU assessment manual for psychopharmacology - william guy - google books [internet]. [cited 2022 May 2]. Available from: https://books.google.co.uk/books?hl=en&id=B4mZEZQRZUEC&oi=fnd&pg=PA6&dq=ECDEU+assessment+manual+for+psychopharmacology&ots=Kp6cffut7D&sig=CU7ysMpY_GnVIs_gRazKs2hTvdw&redir_esc=y#v=onepage&q=ECDEU%20assessment%20manual%20for%20psychopharmacology&f=false.
86. Perrot S, Lantéri-Minet M. Patients' global impression of change in the management of peripheral neuropathic pain: clinical relevance and correlations in daily practice. Eur J Pain. Internet]. 2019 [cited 2022 May 2];23:1117–1128. Available from https://onlinelibrary.wiley.com/doi/full/10.1002/ejp.1378
87. Dose equivalents and changing opioids | faculty of pain medicine [Internet]. [cited 2022 May 2]. Available from: https://fpm.ac.uk/opioids-aware-structured-approach-opioid-prescribing/dose-equivalents-and-changing-opioids.
88. Prescribing in palliative care | medicines guidance | BNF content published by NICE [Internet]. [cited 2022 May 2]. Available from: https://bnf.nice.org.uk/guidance/prescribing-in-palliative-care.html.
89. Cancer Institute N Common terminology criteria for adverse events (CTCAE) version 4.0. 2009 [cited 2022 May 6]; Available from: http://www.meddramsso.com.
90. Beasley TM, Schumacher RE. Multiple regression approach to analyzing contingency tables: post hoc and planned comparison procedures. The Journal of Experimental Education. 2010;64:79–93.
91. Nicholson KJ, Sherman M, Divi SN, et al. The role of family-wise error rate in determining statistical significance. Clin Spine Surg Internet]. 2021 [cited 2022 May 7]; Available from. https://pubmed.ncbi.nlm.nih.gov/34907926/
92. IBM Corp. IBM SPSS statistics for macintosh [Internet]. Armonk NY: IBM Corp; 2021 [cited 2022 May 2]. Available from: https://www.ibm.com/uk-en/analytics/spss-statistics-software.
93. Dotmatics. graphpad prism 9 for macintosh [internet]. San Diego California; 2020 [cited 2022 May 2]. Available from: https://www.graphpad.com/.
94. McLaren J, Swift W, Dillon P, et al. Cannabis potency and contamination: a review of the literature. Addiction. 2008;103:1100–1109.
95. Schneider S, Bebing R, Dauberschmidt C. Detection of pesticides in seized illegal cannabis plants. Anal Methods Internet]. 2013 [cited 2022 May 24];6:515–520. Available from. https://pubs.rsc.org/en/content/articlehtml/2014/ay/c3ay40930a
96. Busse FP, Fiedler GM, Leichtle A, et al. Lead poisoning due to adulterated marijuana in Leipzig. Dtsch Arztebl Int Internet]. 2008 [cited 2022 May 24];105:757–762. Available from. https://pubmed.ncbi.nlm.nih.gov/19623274/
97. Hathaway AD, Comeau NC, Erickson PG. Cannabis normalization and stigma: contemporary practices of moral regulation. Criminology & Criminal Justice [Internet]. 2011 [cited 2022 May 24];11:451–469. Available from. https://journals.sagepub.com/doi/full/10.1177/1748895811415345?casa_token=OZffox17VOIAAAAA%3A0nkqcdpp76dHV3YhFCoPFs8iEPYsrB3UVMpFANBmlfRewGfluD7tEUgL_0qmoPcsgCExpK8lPFin
98. Bottorff JL, Bissell LJL, Balneaves LG, et al. Perceptions of cannabis as a stigmatized medicine: a qualitative descriptive study. Harm Reduct J Internet]. 2013 [cited 2022 May 24];10:1–10. Available from. https://harmreductionjournal.biomedcentral.com/articles/10.1186/1477-7517-10-2
99. Hoge EA, Ivkovic A, Fricchione GL. Generalized anxiety disorder: diagnosis and treatment. BMJ Internet]. 2012 [cited 2022 May 19];345. Available from:. ;:e7500–e7500. https://www.bmj.com/content/345/bmj.e7500
100. Saviola F, Pappaianni E, Monti A, et al. Trait and state anxiety are mapped differently in the human brain. Sci Rep Internet] [cited 2022 May 24];10:1–11. Available from.2020 https://www.nature.com/articles/s41598-020-68008-z
101. Blessing EM, Steenkamp MM, Manzanares J, et al. Cannabidiol as a potential treatment for anxiety disorders. Neurotherapeutics

Internet]. 2015 [cited 2022 May 20];12:825.Available from:. /pmc/articles/PMC4604171/
102. Sharpe L, Sinclair J, Kramer A, et al. Cannabis, a cause for anxiety? A critical appraisal of the anxiogenic and anxiolytic properties. J Transl Med Internet]. 2020 [cited 2022 May 20];18:1–21. Available from. https://translational-medicine.biomedcentral.com/articles/10.1186/s12967-020-02518-2
103. Salviato BZ, Raymundi AM, Rodrigues da Silva T, et al. Female but not male rats show biphasic effects of low doses of Δ9-tetrahydrocannabinol on anxiety: can cannabidiol interfere with these effects? Neuropharmacology. 2021;196:108684.
104. Rapin L, Gamaoun R, El Hage C, et al. Cannabidiol use and effectiveness: real-world evidence from a Canadian medical cannabis clinic. J Cannabis Res Internet] [cited 2022 May 24];3:1–10. Available from. 2021 https://jcannabisresearch.biomedcentral.com/articles/10.1186/s42238-021-00078-w
105. Nielsen S, Picco L, Murnion B, et al. Opioid-sparing effect of cannabinoids for analgesia: an updated systematic review and meta-analysis of preclinical and clinical studies. Neuropsychopharmacology Internet] [cited 2022 May 24];47:1315–1330. Available from. 2022 https://www.nature.com/articles/s41386-022-01322-4
106. Takakuwa KM, Hergenrather JY, Shofer FS, et al. The impact of medical cannabis on intermittent and chronic opioid users with back pain: how cannabis diminished prescription opioid usage. Cannabis Cannabinoid Res Internet]. 2020 [cited 2022 May 24];5:263–270. Available from. https://europepmc.org/articles/PMC7480723
107. Takakuwa KM, Sulak D A survey on the effect that medical cannabis has on prescription opioid medication usage for the treatment of chronic pain at three medical cannabis practice sites. Cureus [Internet]. 2020 [cited 2022 May 24];12. Available from: https://www.cureus.com/articles/41928-a-survey-on-the-effect-that-medical-cannabis-has-on-prescription-opioid-medication-usage-for-the-treatment-of-chronic-pain-at-three-medical-cannabis-practice-sites.
108. Lucas P, Boyd S, Milloy MJ, et al. Cannabis significantly reduces the use of prescription opioids and improves quality of life in authorized patients: results of a large prospective study. Pain Med Internet]. 2021 [cited 2022 May 24];22:727–739. Available from. https://academic.oup.com/painmedicine/article/22/3/727/6053211
109. Goudman L, de Smedt A, Forget P, et al. Determining the minimal clinical important difference for medication quantification scale III and morphine milligram equivalents in patients with failed back surgery syndrome. J Clin Med Internet]. 2020 [cited 2022 May 24];9:1–9.Available from:. /pmc/articles/PMC7700681/
110. Kumar V, Avasthi A, Grover S. Somatosensory amplification, health anxiety, and alexithymia in generalized anxiety disorder. Ind Psychiatry J Internet]. 2018 [cited 2022 May 26];27:47.Available from:. ;:. /pmc/articles/PMC6198604/
111. Lee S, Lam IMH, Kwok KPS, et al. A community-based epidemiological study of health anxiety and generalized anxiety disorder. J Anxiety Disord. 2014;28:187–194.
112. Gómez-Arias B, Crail-Meléndez D, López-Zapata R, et al. Severity of anxiety and depression are related to a higher perception of adverse effects of antiepileptic drugs. Seizure. 2012;21:588–594.
113. MacCallum CA, Russo EB. Practical considerations in medical cannabis administration and dosing. Eur J Intern Med. 2018;49:12–19.
114. Boyko EJ. Observational research opportunities and limitations. J Diabetes Complications Internet]. 2013 [cited 2022 May 25];27:642–648.Available from:. /pmc/articles/PMC3818421/
115. Hróbjartsson A, Emanuelsson F, Thomsen ASS, et al. Bias due to lack of patient blinding in clinical trials. A systematic review of trials randomizing patients to blind and nonblind sub-studies. Int J Epidemiol Internet]. 2014 [cited 2022 May 25];43:1272–1283. Available from.;: . https://academic.oup.com/ije/article/43/4/1272/2952051
116. Wikler A. ASPECTS OF TOLERANCE TO AND DEPENDENCE ON CANNABIS*. Ann N Y Acad Sci. Internet]. 1976 [cited 2022 May 26];282:126–147. Available from https://onlinelibrary.wiley.com/doi/full/10.1111/j.1749-6632.1976.tb49893.x
117. Zdravkovic A, Grote V, Pirchl M, et al. Comparison of patient- and clinician-reported outcome measures in lower back rehabilitation: introducing a new integrated performance measure (t2D). Qual Life Res Internet]. 2022 [cited 2023 Feb 6];31:303–315. Available from. https://link.springer.com/article/10.1007/s11136-021-02905-2
118. Philpot LM, Barnes SA, Brown RM, et al. Barriers and benefits to the use of patient-reported outcome measures in routine clinical care: a qualitative study. Am J Med Qual Internet]. 2018 [cited 2023 Feb 6];33:359–364. Available from. https://pubmed.ncbi.nlm.nih.gov/29258323/
119. Banerjee R, Erridge S, Salazar O, et al. Real world evidence in medical cannabis research. Ther Innov Regul Sci Internet]. 2022 [cited 2022 May 18];56:8–14. Available from https://link.springer.com/article/10.1007/s43441-021-00346-0
•• **A comprehensive review of the importance of real-world evidence in medical cannabis research**