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ORIGINAL RESEARCH

How to ESCAPE from Pain? An Observational Study on Improving Pain and Quality of Life with the Cannamedical® Hybrid Cannabis Extract

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ABSTRACT

Introduction: Chronic pain remains a challenge, with standard therapies often providing inadequate pain relief and causing undesirable side effects. Medicinal cannabis has emerged as promising alternative. This study assessed the impact of a cannabis hybrid extract on pain intensity and quality of life in daily clinical use.
Methods: ESCAPE was an observational study and included patients aged ≥ 18 years with chronic pain in Germany. The primary objective was to evaluate the effectiveness of the Cannamedical® Hybrid Cannabis Extract THC25:CBD25 on pain during four visits (V1–V4) in clinical practice, and key secondary objectives were pain interference and quality of life. Pain intensity was measured using the Numeric Rating Scale (NRS) of the Brief Pain Inventory (BPI) questionnaire. Pain interference was evaluated with the BPI pain interference subscore, and quality of life—particularly physical and mental health—was assessed with the Short Form-12 (SF-12) questionnaire. Additionally, patient and physician satisfaction with the extract was assessed.
Results: The study included 64 patients (50% female) with chronic pain (intention-to treat population; ITT). Cannabis-naïve patients of the ITT were defined as a subgroup and analyzed separately ($N = 35$). Mean (± SD) NRS-assessed pain intensity decreased during the study, in both the ITT (5.46 ± 1.73 at V1 vs. 3.37 ± 2.43 at V4) and in the cannabis-naïve subgroup (5.92 ± 1.34 at V1 vs. 2.37 ± 1.69 at V4). Mean pain interference subscore decreased between V1 and V4 for the ITT (5.39 ± 1.92 vs. 3.38 ± 2.46) and the cannabis-naïve group (5.68 ± 1.46 vs. 2.54 ± 1.99). Physical and mental health improved in both groups and high satisfaction with the hybrid cannabis extract was reported by patients and physicians.
Conclusion: Treatment with the Cannamedical® Hybrid Cannabis Extract THC25:CBD25 in daily clinical practice showed positive effects on patients' pain and quality of life.
Trial Registration: German Clinical Trials Registry identifier DRKS00026906.

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Keywords: Chronic pain; Medicinal cannabis; Pain intensity; Quality of life; Real-world evidence

Key Summary Points

Why carry out this study?

Chronic pain has a high burden on individuals and societies, with a significant impact on personal life and the economy.

Current pharmacological treatment options are limited and include strong opioids, which are associated with significant risks and high healthcare costs.

This observational study evaluated whether a medicinal hybrid cannabis extract could play a multimodal role in improving pain management and quality of life for patients in Germany who are inadequately treated with conventional pharmacological therapies.

What was learned from the study?

In patients with chronic pain treated with the Cannamedical® Hybrid Cannabis Extract THC25:CBD25, pain intensity decreased and quality of life improved during the study.

Our results suggest that medicinal cannabis might be a safe and effective alternative to conventional pharmacological therapies.

As a result of the limitations of this study, in particular the short observation period and the small sample size, there is still a need for long-term observational studies and controlled trials to confirm the cannabis extract's long-term efficacy and safety.

INTRODUCTION

Chronic pain is a widespread health problem, with a high individual and social impact [1]. However, estimates of chronic pain prevalence in populations vary widely and depend on several factors, such as population characteristics, how pain is specifically defined, and which methods are used to assess it [1]. In the UK, prevalence ranges from 13% to 50%, while in the USA, about 20% of adults experience chronic pain [2, 3]. In Germany, chronic pain affects more than 25% of the population [4, 5].

Various factors are associated with the development and prevalence of chronic pain, such as demographic or clinical factors affecting lifestyle and behavior [1]. For example, chronic pain is more common among older adults than it is in younger individuals, mainly because of increased age [2, 6, 7]; and women tend to report chronic pain more frequently than men [8]. Moreover, chronic pain is also linked to the socio-economic background, employment status, and individual lifestyle behaviors [1]. Individuals from less affluent backgrounds and people living in rural areas are more likely to experience pain—which tends to be more severe [9–12]. Furthermore, unemployed people are more likely to have chronic pain than those who are employed, and smokers are reported to have a higher incidence of chronic pain than non-smokers [1, 13–15], with heavy smokers even reporting stronger pain and more painful sites [16–18]. While the influence of such factors on chronic pain is well documented, the role of nutrition and particularly the impact of nutrition-based interventions on chronic pain remain unclear [1]. In a systematic review and meta-analysis, Brain et al. [19] reported several studies, including dietary interventions, suggesting potential benefits of nutrition in chronic pain management. However, the studies were of low quality, and further research is needed to draw definitive conclusions [19–22].

Chronic pain has finally been classified in the International Classification of Diseases 11th Revision (ICD-11) with its own taxonomy and definition [23–25]. It is defined as "pain that persists or recurs for more than three months" [25, 26], and its severity is divided into three grades, based on a 0–10-point Numeric Rating Scale (NRS): mild (1–4), moderate (5–6), and severe (7–10) [27, 28]. Chronic pain initially arises following an injury or illness and several factors have already been identified that affect the duration, intensity, and effects of chronic pain [1, 29]. In addition to pain as the primary

symptom, chronic pain is generally associated with a poor quality of life, limited mobility, and secondary symptoms. These include sleep disorders, and psychological issues like depression and anxiety, worsening the overall mental health status [30–34]. Moreover, chronic pain is associated with multiple comorbid conditions, such as obesity, type II diabetes, and cardiovascular diseases [35]. This combination of primary and secondary health impairments has a significant impact on professional and private life. Besides the impact on personal health, chronic pain also has significant economic burden on society, particularly on health services [36, 37]. Chronic pain leads to higher utilization of healthcare services and causes higher healthcare costs [38–40]; for example, in the USA, it accounts for more than 500 billion USD in healthcare expenditures [41]. Therefore, treatment of chronic pain requires effective treatment strategies.

In a review by Cohen et al. [36], current guidelines recommend an interdisciplinary and personalized treatment approach, integrating pharmacological and non-pharmacological therapies, including self-care, a healthy lifestyle, proper nutrition, psychotherapy, and particularly physical activity and exercise [36, 42–45].

Pharmacological treatment of chronic pain should be based on a patient's diagnosis and needs [36]. Current therapy options for chronic pain include non-opioid pharmacological treatments, along with antidepressants and antiepileptic drugs, and in some cases the administration of opioids [36, 46]. However, opioid therapy carries substantial risks, including dependence, abuse, addiction, and significant side effects, such as constipation, which often lead to treatment discontinuation [47–49]. Therefore, opioids are no longer regarded as first-choice medication and some guidelines do not recommend them for chronic pain treatment in certain populations (e.g., people younger than 30 years) [50]. Moreover, patients with acute and chronic pain who receive opioids tend to incur significant higher healthcare costs, which has an overall impact on the economy [51].

Despite all these pharmacological interventions, many patients with chronic pain still do not achieve adequate pain control with available drugs [52]. For example, approximately 20–40% of patients with chronic neuropathic pain are non-responders, and nearly half of patients with chronic pain overall experience inadequate pain relief [53]. Given the limitations of current pharmacological treatments and their associated risks, there is a need for alternative therapies.

Medicinal cannabis, particularly in the form of cannabis extracts, has emerged as a promising option for the treatment of chronic pain. In Germany, legislative changes in 2017 facilitated the prescription of medicinal cannabis to treat patients with cannabis-derived medicines under certain conditions [54].

Among cannabinoids, tetrahydrocannabinol (THC) and cannabidiol (CBD) are the best researched in terms of therapeutic use [55, 56]. In this context, a combination of THC and CBD appears particularly beneficial, as CBD can mitigate some of the undesirable effects of THC (e.g., intoxication, sedation, tachycardia) while enhancing its therapeutic effects [57, 58]. Furthermore, studies indicated that a THC:CBD ratio of 1:1 is both effective and well tolerated in treating chronic pain [59–61].

The effectiveness of medicinal cannabis in relieving pain and improving quality of life in patients with chronic pain has already been reported in several studies [62–64], with oral formulations having a superior effect on pain relief than oromucosal routes of administration [65]. Moreover, systematic reviews and meta-analyses of randomized controlled trials (RCTs) on cannabinoids for treatment of non-cancer-related pain revealed statistically significant reductions in pain compared to placebo [65, 66]. However, it must be noted that differences exist when comparing the results of RCTs and observational studies [67]. Other research demonstrated that medicinal cannabis also improves sleep, appetite, depression and anxiety, and overall quality of life [68–70]. Additionally, studies increasingly indicate that the use of medicinal cannabis for chronic pain also has a positive effect on opioid usage and that their dosage can be reduced. In a long-term study from 2020, 30 out of 61 patients who had been suffering from chronic pain for a median

of 11 years were able to stop taking opioids completely after a median of 6.4 years [71]. Thus, the multimodal use of medicinal cannabis can improve pain management and quality of life of inadequately treated patients.

Despite these promising findings and the rapidly growing number of clinical studies, clinical evidence on medicinal cannabis—for treatment of non-cancer chronic pain—remains limited [65].

To address this, the ESCAPE non-interventional, observational trial was conducted. In this study, we assessed the impact of medicinal cannabis on pain and quality of life in a real-world, non-standardized population in Germany. We investigated whether the Cannamedical® Hybrid Cannabis Extract THC25:CBD25 (25 mg/mL each) could play a multimodal role in improving pain management and quality of life for patients who are inadequately treated with conventional therapies in daily clinical routine.

METHODS

Study Design

ESCAPE was a non-interventional, multicenter, observational study. It was planned to enroll approximately 500 patients with chronic pain at 200 medical practices in Germany. Patients who met the following criteria were included: aged ≥ 18 years; presence of chronic pain; history of unsuccessful previous pain therapies due to side effects, insufficient dosage, interactions or pre-existing conditions, or allergic reactions; no previous treatment with the Cannamedical® Hybrid Cannabis Extract THC25:CBD25; prescription of medicinal cannabis independently of study participation; signed informed consent form. Exclusion criteria were existing recreational cannabis or drug use within the last 6 months; presence of schizophrenia, psychosis, or other psychiatric illnesses as underlying conditions; known allergies to ingredients or carriers of the study medication; pregnancy or breastfeeding women; women planning pregnancy during study participation; simultaneous participation in another study.

Treatment Schedule

Patients were prescribed the Cannamedical® Hybrid Cannabis Extract THC25:CBD25 (25 mg/mL each) as part of routine clinical care. Each patient was observed for approximately 6 months, during which up to four visits were scheduled at the discretion of the treating physician at site. Data collection occurred at the baseline visit (V1, day 0) and at three subsequent visits (V2–V4).

Endpoints/Outcome Measures

Data were collected through a combination of physician assessments and patient-reported outcomes to evaluate both pain experience and quality of life in patients within a real-world clinical setting. Standardized and validated instruments were used, including the Brief Pain Inventory Short Form (BPI-SF) questionnaire, the 11-point NRS, and the Short Form 12 (SF-12) questionnaire.

The primary outcome was the change in average pain intensity in patients with chronic pain treated with the Cannamedical® Hybrid Cannabis Extract THC25:CBD25. Pain intensity was assessed with the 11-point (range 0–10) NRS, embedded within the BPI-SF (i.e., the four severity items, questions 3–6). Pain scores were calculated as the mean of responses to questions 3–6 of the BPI-SF. Baseline NRS values recorded at V1 were compared with those at subsequent visits (V2, V3, and V4) to evaluate the efficacy of the cannabis extract during the study.

Secondary outcomes comprised pain interference and patients' quality of life, particularly the physical and mental health status. Pain interference was scored as the mean of responses to questions 9–15 (range 0–10) of the BPI-SF. Changes in physical and mental health status were assessed by the mean scores of the physical component summary (PCS) and the mental component summary (MCS) of the SF-12 questionnaire.

Additionally, physician and patient satisfaction with the therapy was assessed at the final visit (V4). Patients and physicians were asked to rate their satisfaction with the Cannamedical® Hybrid Cannabis Extract THC25:CBD25 on a scale of 1–10, and indicate whether they would recommend it to others.

Data Collection

Physicians at participating centers were instructed to record all data in patient files and corresponding paper case report forms (CRFs). Completed CRFs were transferred into an electronic study database (eCRF). Before entry into the eCRF, data in the paper CRFs were visually checked for errors by qualified sponsor personnel. Queries were made to participating centers if necessary to ensure data accuracy.

At the baseline visit (V1, day 0), patients' demographics, health insurance status, medical history, indication for cannabis therapy, medication dosage, and premedications and comedications were recorded and patients rated their pain intensity and quality of life. Pain intensity was assessed using the 11-point NRS, and quality of life was evaluated using the self-reported BPI-SF and SF-12 questionnaires.

The BPI-SF measures both pain intensity and pain interference, assessing various dimensions of daily functioning, such as general activity, mood, walking ability, work performance, interpersonal relationships, sleep, and enjoyment of life [72]. The SF-12 focuses on aspects related to vitality, social functioning, emotional roles, and overall well-being, yielding two summary scores: the PCS-12 and the MCS-12 with scores ranging from 0%, being the lowest, to 100% [73]. Outcomes of PCS-12 and MCS-12 were analyzed separately.

Subsequent visits (V2–V4) were scheduled at intervals determined by the treating physician. At visits V2 and V3, we assessed pain intensity (NRS), quality of life (BPI-SF and SF-12), and any changes in study medication or premedication and comedication dosages. Additionally, updates on the status of pre-existing and concomitant diseases were collected to track potential changes in patient health. Patients were also asked to indicate whether the therapy would be continued or discontinued—with specific reasons provided in case of therapy discontinuation.

Additional assessments at V4 included patient and physician satisfaction with the therapy, recommendations regarding the use of the Cannamedical® Hybrid Cannabis Extract THC25:CBD25, and update on health insurance status.

Adverse events (AEs) were systematically recorded by patient self-report during the study to evaluate the safety profile of the treatment. A summary of assessments performed at each visit is presented in Table 1.

Ethics Compliance Statement

ESCAPE was a non-interventional, national, multicenter, observational study with the prescription drug Cannamedical® Hybrid Cannabis Extract THC25:CBD25 (25 mg/mL each) conducted in Germany. The study was conducted in accordance with the principles of the Declaration of Helsinki of 1964 and its later amendments, the German Medicinal Products Act, the professional code of conduct for physicians, and the General Data Protection Regulation (GDPR) in their respective valid versions.

In compliance with the German Medicinal Products Act, the study was notified to the Federal Institute for Drugs and Medical Devices (German BfArM), the National Association of Statutory Health Insurance Physicians, the National Association of Statutory Health Insurance Funds, and the Association of Private Health Insurers. Ethical approval was obtained from the coordinating Ethics Committee at the Medical Association of North Rhine (Application number 2021414) and the local ethics committees involved (list of ethics committees in the supplementary material). The study was registered with the German Clinical Trials Registry (DRKS00026906). All patients gave written informed consent before participating.

Table 1 Summary of assessments at each visit

Assessment	Visit 1 (baseline)	Visit 2	Visit 3	Visit 4 (final)
Informed consent	X			
Inclusion and exclusion criteria	X			
Demographics and health insurance status	X			X
Medical history and concomitant diseases	X	X	X	X
Prior medicinal cannabis use	X			
Pain intensity (BPI-SF and NRS)	X	X	X	X
Quality of life assessments (BPI-SF, SF-12)	X	X	X	X
Study medication dosage	X	X	X	X
Premedications and comedications	X	X	X	X
Changes in medication since last visit		X	X	X
Adverse events		X	X	X
Continuation of therapy assessment		X	X	X
Patient and physician satisfaction				X
Recommendations for therapy				X

BPI-SF Brief Pain Inventory Short Form questionnaire, *NRS* Numeric Rating Scale, *SF-12* Short Form 12 questionnaire

Statistical Analysis

The statistical analysis included all patients enrolled in the study (intention-to treat population, ITT). Cannabis-naïve patients of the ITT were defined as a subgroup and analyzed separately.

Assuming a standard deviation of 2.0 to 2.2 points in pain intensity (measured using the BPI-SF), the width of the 95% confidence interval for the pre/post comparison of pain intensity could be estimated within 0.3 scale units with a probability of 95% (requiring 351 patients at a standard deviation of 2.0 and 425 patients at a standard deviation of 2.2).

With 500 patients effect sizes of approximately $d=0.15$ could be demonstrated with 80% power for pre/post comparisons of continuous parameters. The frequency of dichotomous traits could be estimated with a precision of 0.06 and a power greater than 99% if the true occurrence rate was between 10% and 90%.

Two-sided p values below 0.05 were regarded as statistically significant. The primary focus was on the intensity of pain over time, particularly after 1 and 3 months. Participants were included in the analysis if a pain measurement was available after 1 month (± 7 days) or after 3 months (± 14 days). If data were sparse for these time points, linear interpolation was considered. The same approach was applied to other parameters.

Continuous or quasi-continuous variables with approximately symmetrical distributions (skewness between − 1 and + 1) were analyzed using paired t tests. Mean differences with 95% confidence intervals and exploratory p values were calculated.

Descriptive statistics—including the number of observations, mean, standard deviation, minimum, median, and maximum—were reported for all evaluated parameters. Subgroups were predefined in the statistical analysis plan, and comparisons were made using t tests or analysis of variance (ANOVA) for continuous variables and

chi-square tests or logistic regression for categorical variables.

Selected AEs were recorded using a predefined list (vomiting, constipation, disturbances in vigilance, headache, nausea, sweating, dizziness, and others) and categorized by intensity (mild, moderate, severe). Absolute and relative frequencies were presented.

Statistical analyses were performed with Statistical Analysis Software (SAS®) version 9.4.

RESULTS

Demographics and Baseline Characteristics

A total of 64 patients at eight study centers in Germany were enrolled between May 2022 and February 2023, and the study was completed on August 2023. All enrolled patients provided written informed consent before inclusion.

Patients' demographics and baseline characteristics, including age, gender, ethnicity, occupational status, marital status, and body mass index (BMI), are shown in Table 2. Most patients were Caucasian (95%), with an equal distribution of men and women. Mean (± SD) age was 55.72 ± 14.29 years, and mean BMI was 26.37 ± 4.80 kg/m^2. A significant proportion were retired (41%), and most patients were married (58%) and employed (53%).

Health Insurance Status

Of the 64 patients, nearly all had health insurance coverage, with data missing for only one patient (Table 3). The largest group was covered by a statutory health insurance (76%).

Indications for Medicinal Cannabis Use

The most common indication for medicinal cannabis use was chronic back pain, reported by 42% of patients, with bone and joint diseases and other conditions each noted by 31% of patients (Table 4). Sixteen percent of patients reported using medicinal cannabis to manage each of the following indications: fibromyalgia,

Table 2 Patients' demographics and baseline characteristics

Variable	ITT population (*N* = 64)
Age [years]	
N	64
Mean (SD)	55.72 (14.29)
Gender, *N* (%)	
Female	32 (50.00%)
Male	32 (50.00%)
Ethnicity, *N* (%)	
Caucasian	61 (95.31%)
Asian	1 (1.56%)
Other	2 (3.13%)
Profession, *N* (%)	
Employed	34 (53.13%)
Trainee	1 (1.56%)
Student	1 (1.56%)
Retired	26 (40.63%)
Unemployed	2 (3.13%)
Marital status, *N* (%)	
Single	11 (17.19%)
In partnership but not married	8 (12.50%)
Married	37 (57.81%)
Divorced	3 (4.69%)
Living apart	1 (1.56%)
Widowed	4 (6.25%)
BMI	
N	64
Mean (SD)	26.37 (4.80)
Min	15.00
Median	26.00
Max	38.60

BMI body mass index, *ITT* intention-to treat, *N* number of patients, *SD* standard deviation

Table 3 Health insurance status

Variable	*N* (%)
Does the patient have health insurance?	
Yes	63 (100.00%)
Missing	1
If yes, which health insurance company is the patient insured with?	
Statutory health insurance fund	48 (76.19%)
Private health insurance fund	15 (23.81%)
Missing	1

Percentages are based on the 63 patients who reported having health insurance

N number of patients

migraines or cluster headaches, and post-traumatic or postoperative pain. Multiple indications were often reported by patients as a result of their multimorbidities.

Table 4 Indications for medicinal cannabis use

Indication	*N* (%)
Chronic back pain	27 (42.19%)
Diabetic neuropathy	5 (7.81%)
Fibromyalgia	10 (15.63%)
Bone and joint disorders	20 (31.25%)
Cancer-associated pain	3 (4.69%)
Migraine/cluster headaches	10 (15.63%)
Post-traumatic and postoperative pain	10 (15.63%)
Post-zoster neuralgia	1 (1.56%)
Pain in chronic inflammatory bowel diseases	3 (4.69%)
Pain in multiple sclerosis	6 (9.38%)
Other	20 (31.25%)

Multiple answers were possible; therefore, percentages do not sum to 100%

N number of patients

Study Medication Intake

Study medication data for the ITT population are summarized in Table 5. Out of the 64 patients, medication intake data were available for 55 patients. Patients showed significant variability in treatment duration, cumulative dose, and average daily dose: median (range) treatment duration was 71 days (4–220 days), with a median cumulative dose of 730.00 mg (47.50–14,775.00 mg), and a median daily dose of 10.00 mg (2.50–84.90 mg).

Pain Intensity Assessed with the 11-Point NRS

The mean (±SD) NRS scores over time for the ITT group and the cannabis-naïve population are presented in Fig. 1. In the ITT group, we observed a steady decrease in NRS-assessed pain intensity during the study (Fig. 1a), decreasing from V1 to V2 (5.46±1.73 vs. 4.76±2.06), and from V3 to V4 (4.52±2.49 vs. 3.37±2.43). In cannabis-naïve patients NRS-assessed pain intensity also decreased, particularly between V1 and V2 followed by stabilization and a further decrease (Fig. 1b). Mean (±SD) NRS scores decreased from V1 to V2 (5.92±1.34 vs. 3.55±1.70), and then further decreased from V3 to V4 (3.56±1.58 vs. 2.37±1.69).

Pain Interference Assessed with the BPI Interference Score

Mean (±SD) interference subscore changes are summarized in Fig. 2. Our analysis showed a trend toward improved pain interference in daily life among patients of the ITT population during the study, with greatest improvement between V3 and V4 (4.60±2.79 vs. 3.38±2.46; Fig. 2a). A similar pattern was observed for cannabis-naïve patients at V3 and V4 (4.38±3.15 vs. 2.54±1.99; Fig. 2b).

Physical Health Assessed with SF-12

Mean (±SD) PCS-12 scores for the ITT population and cannabis-naïve patients are shown in Fig. 3. We observed a mild improvement in physical health among patients of the ITT

Table 5 Medication intake

Variable	ITT population ($N = 64$)
Number of days on which the medication was taken	
N	55
Mean (SD)	99.00 (59.90)
Median	71.00
Min	4.00
Max	220.00
Missing	9
Cumulative dose [mg]	
N	55
Mean (SD)	1738.90 (2853.60)
Median	730.00
Min	47.50
Max	14,775.00
Missing	9
Mean dose [mg]	
N	55
Mean (SD)	14.49 (14.99)
Median	10.00
Min	2.50
Max	84.90
Missing	9

ITT intention-to treat, *N* number of patients, *SD* standard deviation

population during the study (Fig. 3a), with mean (±SD) PCS-12 scores increased from V1 to V4 (30.38 ± 6.57 vs. 36.54 ± 11.46). In cannabis-naïve patients, a considerable improvement in physical health was recorded between V2 and V3 (35.84 ± 7.00 vs. 48.94 ± 6.32; Fig. 3b). However, PCS-12 scores decreased from V3 to V4 (48.94 ± 6.32 vs. 39.91 ± 11.39), while at the same time the variability increased.

Mental Health Assessed with SF-12

Mean (±SD) MCS-12 scores in the ITT population increased from V1 to V2 (37.94 ± 10.81 vs. 44.17 ± 12.53; Fig. 4a), and remained relatively stable afterwards at V3 (44.43 ± 12.75). Cannabis-naïve patients also reported an improvement in mental health between V1 and V2 and V3 (34.23 ± 6.22 vs. 42.33 ± 11.59 vs. 45.84 ± 12.89; Fig. 4b). We observed a slight decline in mental health between V3 and V4 in the ITT population (44.43 ± 12.75 vs. 42.46 ± 11.47) and in the cannabis-naïve group (45.84 ± 12.89 vs. 43.47 ± 11.72), with score variability increased in the cannabis-naïve group at V4.

Safety

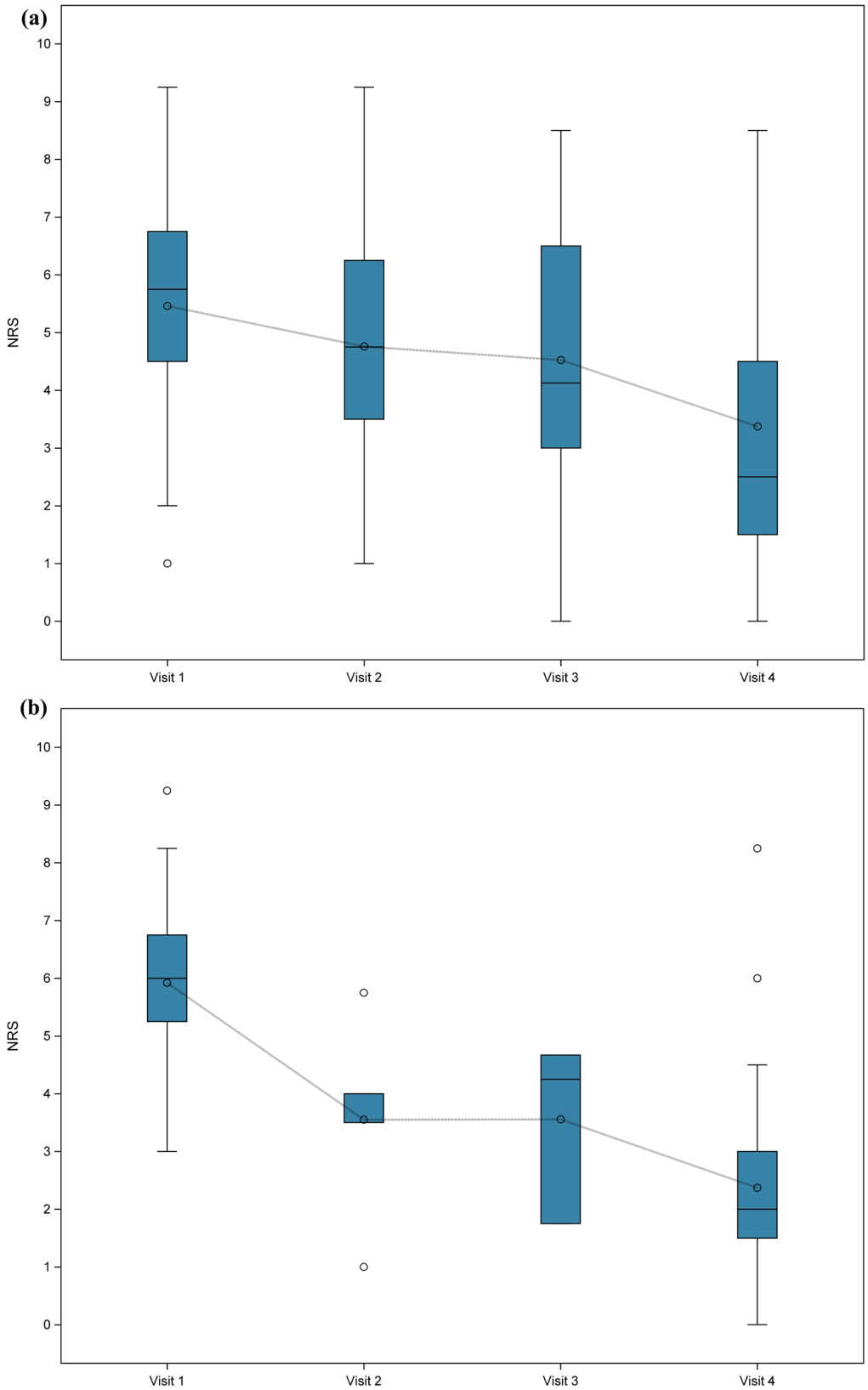
Three AEs—loss of appetite, dizziness, and nausea—were reported for two patients within the ITT population during the study (Table 6). No serious AEs (SAEs) occurred.

Satisfaction and Recommendations

Patient and physician satisfaction and recommendations regarding treatment with the cannabis hybrid extract are summarized in Table 7. Both physicians and patients rated their satisfaction, with physicians reporting a mean (±SD) score of 7.60 ± 1.94 and patients reporting a mean score of 7.45 ± 2.02. Most physicians (94%) and patients (77%) would recommend the treatment.

DISCUSSION

ESCAPE demonstrated that patients in the ITT population and the cannabis-naïve subgroup experienced less pain during treatment with the Cannamedical® Hybrid Cannabis Extract THC25:CBD25. Furthermore, patients' pain interference decreased, along with improvements in both physical and mental health. Our results also showed that treatment with the extract is safe, with only three AEs occurred in two patients. Satisfaction rate was high in


(a)
NRS
10
9
8
7
6
5
4
3
2
1
0
Visit 1
Visit 2
Visit 3
Visit 4
(b)
NRS
10
9
8
7
6
5
4
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2
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Visit 1
Visit 2
Visit 3
Visit 4

◂**Fig. 1** Pain intensity over time. Changes in mean Numeric Rating Scale (NRS) scores during the study for **a** the intention-to-treat (ITT) population and **b** cannabis-naïve patients

patients and physicians. Taken together, the results suggest that medicinal cannabis might be a safe alternative for patients who are inadequately treated with conventional therapies.

Study Population

ESCAPE included adults with a mean (± SD) age of 55.72 ± 14.29 years, and a mean BMI of 26.37 ± 4.80 kg/m^2, indicating that most patients fell within the overweight or pre-obesity range (BMI 25.00–29.9 kg/m^2)—according to the WHO classification [74]. The demographic profile in our study is similar to what is seen in other analyses. For example, most patients in the included studies of the meta-analysis by Brain et al. [19] were female, aged > 50 years, and overweight. Moreover, Tardif et al. [75] reported that in Australian pain clinics, approximately 30% of patients with chronic pain were classified as overweight, 37% as obese, with a mean age of 52.4 years and 59% being female.

It is well known that prevalence of chronic pain is higher in women than in men [8, 76]; however, an observational study investigating the efficacy of medicinal cannabis for chronic pain treatment showed a higher proportion of men than women in its study population [62]. In contrast, the ESCAPE study revealed a balanced gender distribution, with 50% female, indicating that its demographic profile aligns closely with the "typical" chronic pain population.

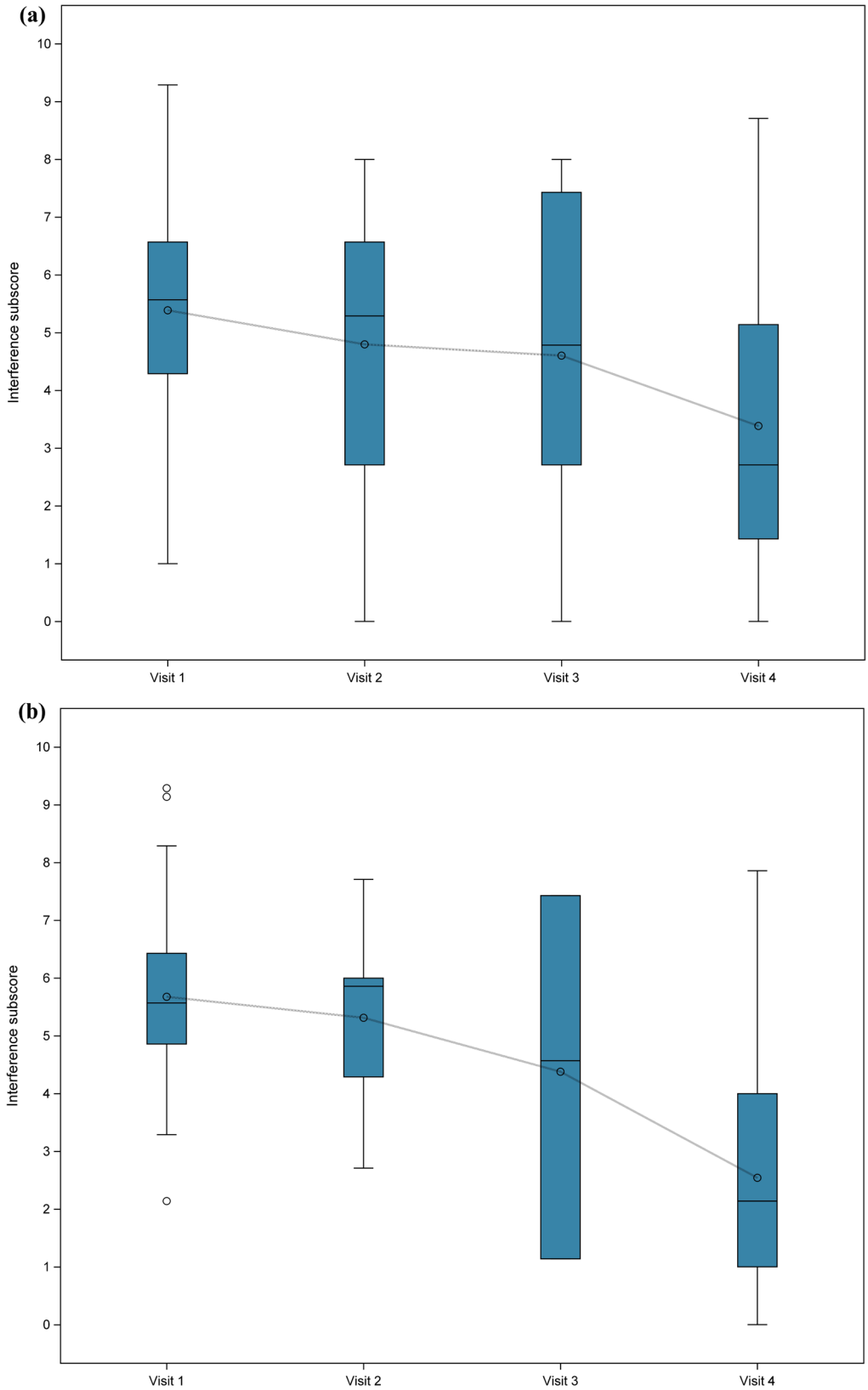
The correlation in age and BMI also highlights common challenges in treating chronic pain, since increased age and a higher BMI are often associated with more severe pain, reduced mobility, and a higher prevalence of comorbidities—all of which can affect treatment outcomes [1, 77].

Pain Intensity Over Time

ESCAPE used patient-reported outcome measures to assess pain intensity, pain interference with daily life and to assess physical and mental health during the observation period.

In discussing the NRS outcomes across multiple visits, we observed a substantial reduction in patient-reported pain intensity over time in both groups. At baseline mean NRS scores were 5.46 ± 1.73 (ITT) and 5.92 ± 1.34 (cannabis-naïve group), indicating moderate pain, and 3.37 ± 2.43 (ITT) and 2.37 ± 1.69 (cannabis-naïve group) at V4, indicating mild pain [27, 28]. The observed 2.09/38% (ITT) and 3.55/60% (cannabis-naïve group) reduction in NRS scores was statistically significant ($p < 0001$) and is considered clinically significant [78–80]. This is in line with other findings summarized in the review by Lynch and Campbell [66], showing that cannabinoids are effective analgesics in chronic pain, particularly oral cannabinoid formulations within short treatment durations. For example, recently published data showed that using medicinal cannabis for 3 months significantly reduced pain intensity in patients with chronic pain [63]. Similar results have also been reported in an open-label study over a 6-month period [62]. Therefore, our findings in ESCAPE are consistent with previous studies, indicating that cannabinoids might provide a cumulative analgesic effect.

The efficacy of medicinal cannabis on pain intensity has also been evaluated over longer periods. Aviram et al. [68] assessed in a multicenter, prospective, long-term study the effect of medicinal cannabis on chronic pain and associated symptoms, and reported a statistically significant reduction in pain intensity over 12 months, with an average reduction of 20% from baseline. While the observed analgesic effect was modest, the study supports that cannabinoids can provide stable, long-term pain relief for patients with chronic pain. Moreover, in a prospective observational study, patient treatment with THC revealed significant improvements in BPI-SF assessed pain intensity at 1 month, and remaining at 12 months [64]. However, as a result of the 6-month observation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◂**Fig. 2** Pain interference over time. Changes in mean Brief Pain Inventory (BPI) interference scores during the study for **a** the intention-to-treat (ITT) population and **b** cannabis-naïve patients

period in ESCAPE, we cannot yet make any statements on the long-term efficacy of the Cannamedical® Hybrid Cannabis Extract.

Pain Interference

Our results demonstrated that in both groups BPI pain interference subscores decreased over time. These results are consistent with the findings of other observational studies [63, 64]. Those studies showed significant reductions in pain interference, with patients experiencing less impairment in daily activities. The reduction in pain interference implies that medicinal cannabis can improve patients' physical functionality and quality of life, enabling greater independence and better participation in daily life [63]. The study by Aviram et al. [68] also demonstrated improvements in pain interference, with disability-related scores decreasing by approximately 19%. Similar results have also been reported by Haroutounian et al. [62], with significant improvements in BPI interference subscores from baseline.

Quality of Life

Furthermore, our findings indicate that treatment with medicinal cannabis improves both physical and mental health in patients with chronic pain. In the present analysis, physical and mental health scores were low at baseline, with mean PCS-12 scores of 30.38 ± 6.57 (ITT) and 35.84 ± 7.00 (cannabis-naïve group) and mean MCS-12 scores of 37.94 ± 10.81 (ITT), and 34.23 ± 6.22 (cannabis-naïve group). The observed improvements in PCS-12 scores during the study are likely related to lower pain intensity, as patients who experience less pain are suggested to have better physical activity in everyday life. This is in line with other research, suggesting that the improvement in physical health is related to the pain relief effect [64].

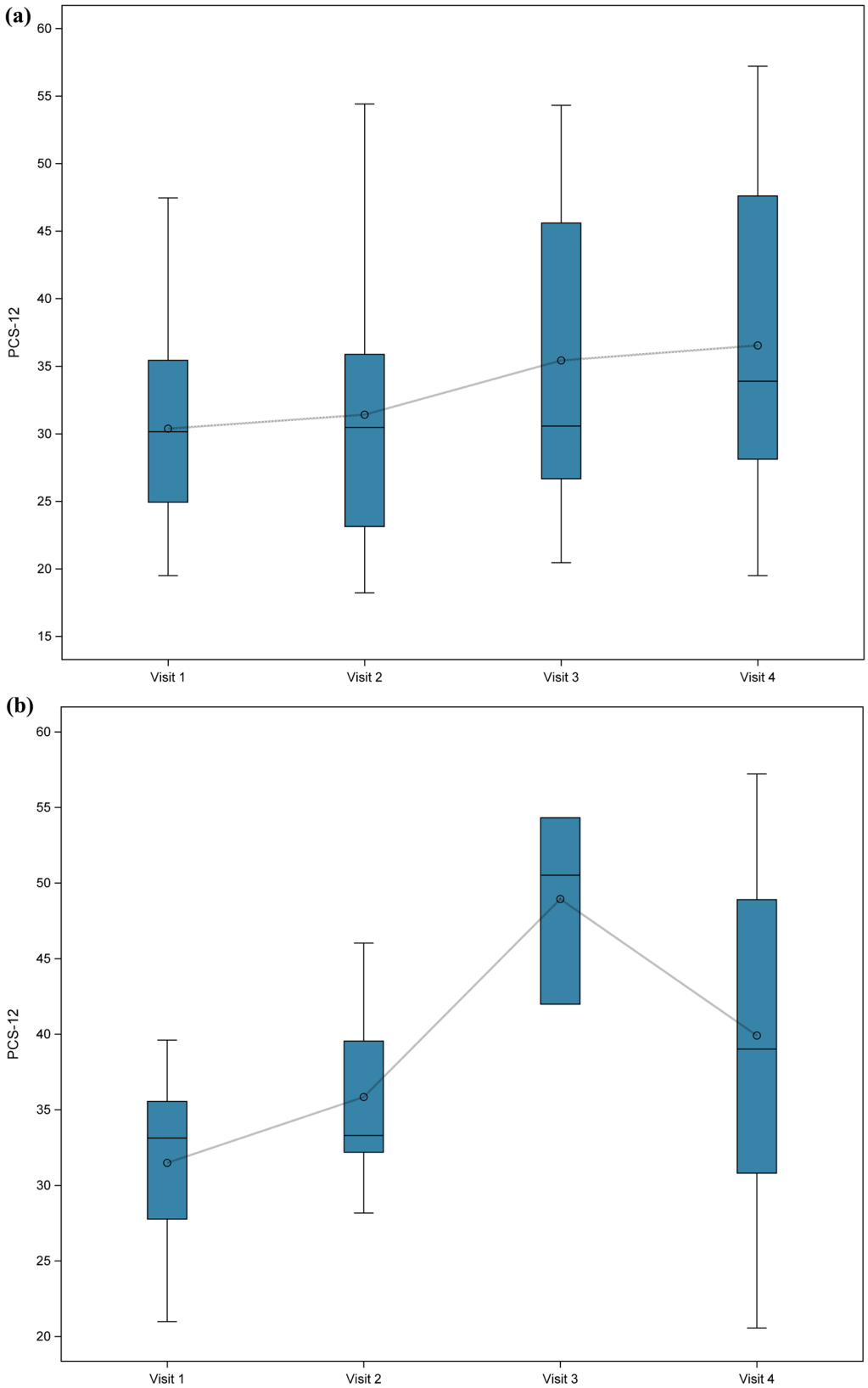
In ESCAPE, MCS-12 scores of patients showed a noticeable increase from baseline to the second visit, stabilizing at the subsequent visit and then decreased slightly at the final visit. These initial mental health improvements have also been reported in other studies, where cannabis use for chronic pain is associated with moderate, often short-to-midterm mental health benefits [62, 63, 66, 68]. Lynch and Campbell [66] reported in their systematic review of RCTs that, in addition to moderate pain relief, cannabinoids are often associated with mental health benefits, including reduced anxiety and improved sleep, which can facilitate the psychological burden of chronic pain.

Thus, our findings are consistent with the broader literature, suggesting that while cannabinoids do not dramatically improve mental health, they may provide additional benefits that reduce psychological burden and support quality of life of patients with chronic pain.

Safety Profile

Frequency of AEs was low in our study. Only three adverse events—dizziness (mild), nausea (moderate), and appetite loss (mild)—were reported and we did not observe any serious adverse event during the study.

AEs such as those observed in ESCAPE are common and appear to occur at a relatively low frequency, with SAEs being rare [63, 64, 66, 68, 81]. Lynch and Campbell's [66] systematic review supports this observation, as cannabinoids have generally been well tolerated in chronic pain populations, with mild AEs, typically being self-limiting and not leading to significant discontinuation rates. However, it must be noted that the observation period in ESCAPE was low and studies investigating long-term AE effects of cannabinoids are limited. Therefore, we cannot yet confirm that the safety profile of the Cannamedical® Hybrid Cannabis Extract is maintained over longer observation periods. Overall, our findings are in line with current literature supporting a favorable safety profile for cannabinoids in chronic pain, suggesting that despite mild and manageable AEs, the benefits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◂**Fig. 3** Physical health status over time. Change in physical health status from visit 1 to visit 4 for **a** the intention-to-treat (ITT) population and **b** cannabis-naïve patients

may outweigh the risks for patients seeking alternative or adjunct pain management.

Limitations

In ESCAPE, several factors must be considered that might impact the interpretation and generalizability of our findings.

First, ESCAPE was an observational study without a control group, thus lacking the ability to establish causative effects of cannabinoid treatment on observed outcomes. Without a comparative placebo or active control group, our findings may reflect underlying patient variability rather than direct effects of the Cannamedical® Hybrid Cannabis Extract. Additionally, the included study population was taken very broad, such that possible effects were diluted by the heterogeneity of the study population.

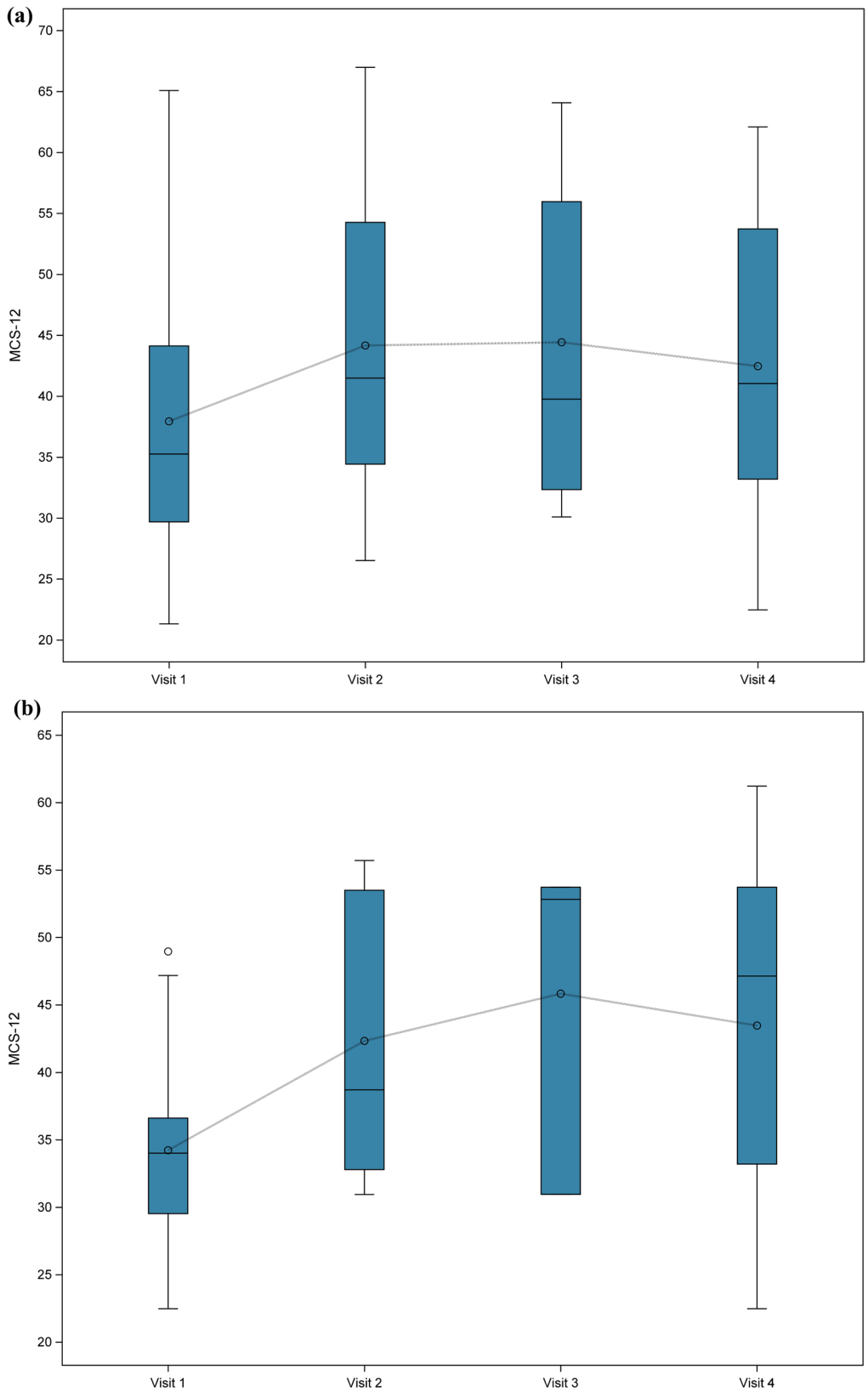
Second, the study's limited sample size of 64 patients reduces statistical power and limits the ability to detect smaller effect sizes, making it challenging to generalize the results to broader chronic pain populations. At the time the study was conducted, patients with statutory health insurance required prior authorization for cost coverage, creating a major challenge for both physicians and patients. This administrative process contributed significantly to a longer recruitment period. Consequently, ESCAPE was completed with a smaller sample size to enable analysis and publication of results. The aim was to provide physicians, who had not previously prescribed medicinal cannabis extracts to patients, with clear evidence on their efficacy and safety, thereby facilitating prescribing decisions.

The small cohort in ESCAPE may also be insufficient to fully capture the variability in patient response to the extract, especially given the observed large individual variation typically seen in pain management. Additionally, the short observation period of 6 months does not provide any insights into the long-term efficacy and safety of the Cannamedical® Hybrid Cannabis Extract. Chronic pain management often requires prolonged treatment, and without a longer follow-up period, conclusions regarding sustained efficacy, adverse effects, addictive behavior and abuse remain challenging. In this context, in July 2022, the German BfArM published the final report for the companion survey on the use of cannabis medicinal products [82]. Approximately 17,000 complete data records on treatments with cannabis flowers and extracts as well as dronabinol, nabilone, and Sativex® were included in the evaluation between April 2017 and March 2022. The companion survey showed that medicinal cannabis is well tolerated in the long term, with only mild to moderate AEs reported. The reported AEs in the survey were often likely due to incorrect dosing. Furthermore, no deaths or addictive behavior could be identified [82]. However, the BfArM emphasizes the need to conduct more clinical trials to further evaluate the efficacy and safety of cannabis medicines.

Third, the observed high variability in medication intake across patients complicates interpretation of the dose–response relationship and the consistency of treatment effects. This variability may mask specific dose-dependent responses and contribute to a heterogeneous outcome profile, further challenging the trial's internal validity.

It must also be noted that patients' weight might have an impact on overall efficacy of the Cannamedical® Hybrid Cannabis Extract. Cannabinoids, such as THC and CBD, are lipophilic and are rapidly absorbed in fatty tissue, with an impact on pharmacokinetics [83–85]. In their study, Aviram et al. [68] hypothesized that a high BMI might result in lower plasma concentrations of the active compounds, having worse outcomes. Therefore, it would be of interest to further investigate the association between BMI and the analgesic effect of medicinal cannabis. For example, assessing the efficacy of the Cannamedical® Hybrid Cannabis Extract THC25:CBD25 in patients with obesity compared to patients with normal weight.

Taken together, these limitations highlight the need for future studies with larger sample sizes,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◂**Fig. 4** Mental health status over time. Change in mental health status from visit 1 to visit 4 for **a** the intention-to-treat (ITT) population and **b** cannabis-naïve population

control groups, longer observation periods, and standardized dosing to better understand the efficacy, safety, and optimal use of cannabinoids in chronic pain treatment.

Strengths

In contrast to RCTs, with their restrictive inclusion and exclusion criteria and fixed medication and visit schemes, an observational trial provides insights that more closely reflect real-world outcomes and patient experiences. An observational trial mirrors daily routine, taking into account individual medication intake and dosages, and measurement of multiple outcome variables using self-reporting questionnaires. In our study, we observed a high variability in medication intake and dosage of the Cannamedical® Hybrid Cannabis Extract, reflecting the diversity of treatment regimens followed by patients—which is often limited in RCTs. Moreover, as discussed earlier, the analyzed study population in ESCAPE might represent the "typical" patient with chronic pain, supporting generalizability of our results to the wider chronic pain population.

Furthermore, ESCAPE used comprehensive outcome measures. Besides the primary outcome, impact on pain intensity, we also assessed pain interference and quality of life, particularly physical health and mental health. Both aspects play an important role in chronic pain management and particularly personal life. Mental health issues, such as depression, anxiety, and negative thoughts, are all linked to chronic pain development and having worse outcomes [1, 86–89]; whereas chronic pain is directly associated with impaired physical function in daily life [30].

Overall, ESCAPE's design and focus provides valuable insights into how patients with chronic pain actually use medicinal cannabis and what impact the treatment has on everyday chronic pain management.

CONCLUSION

This non-interventional study observed the pain experience and quality of life in patients with chronic pain treated with the Cannamedical® Hybrid Cannabis Extract THC25:CBD25 (25 mg/mL each) over a period of up to 6 months in

Table 6 Summary of adverse events

Adverse event (intensity)	Patients in ITT population reporting AE ($N=64$)	nAEs (%)
AEs	2 (3.13%)	3 (100.00%)
Appetite loss (mild)	1 (1.56%)	1 (33.33%)
Dizziness (mild)	1 (1.56%)	1 (33.33%)
Nausea (moderate)	1 (1.56%)	1 (33.33%)

AE adverse event, *ITT* intention-to treat, *N* number of patients, *nAEs* number of adverse events

Table 7 Satisfaction and recommendation with Cannamedical® Hybrid Cannabis Extract treatment

Variable	Patients in ITT population ($N=64$)
From physicians' perspective: how satisfied are you with the treatment with Cannamedical® Extract (scale 1–10)?	
N	47
Mean (SD)	7.60 (1.94)
Median	8.00
Range	2.0–10.00
Missing	17
From physicians' perspective: would you recommend the treatment with Cannamedical® Extract?	
Yes	44 (93.62%)
Maybe/partially	3 (6.38%)
Missing	17
From patients' perspective: how satisfied are you with the treatment with Cannamedical® Extract (scale 1–10)?	
N	47
Mean (SD)	7.45 (2.02)
Median	8.00
Range	3.0–10.00
Missing	17
From patients' perspective: would you recommend the treatment with Cannamedical® Extract?	
Yes	36 (76.60%)
No	1 (2.13%)
Maybe/partially	10 (21.28%)
Missing	17

ITT intention-to treat, *N* number of patients, *SD* standard deviation

routine clinical practice. Our results suggest that the Cannamedical® Hybrid Cannabis Extract may be a safe and effective alternative to conventional pharmacological therapies for treatment of chronic pain. Patients experienced less pain, along with improvements in both physical and mental health, which positively impacted their daily lives. However, as a result of this study's limitations, in particular the short observation period, the small sample size, and the high variability, there is a need for long-term observational studies and controlled trials to confirm the Cannamedical® Hybrid Cannabis Extract's long-term efficacy and specific effects.

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Author Contribution. All listed authors fulfill the recommendations of the International Committee of Medical Journal Editors (ICMJE) for authorship. Yvonne Wagner had the idea for the study. Joachim Nadstawek, Yvonne Wagner, Ines Samel, Kristina Probst, Lukas Schollenberger and Christian Ruckes contributed to study conceptualization and preparation. Joachim Nadstawek was head of study. Yvonne Wagner, Ines Samel and Lukas Schollenberger supervised the study. Statistical analysis and interpretation of the data was performed by Christian Ruckes. The first draft of the manuscript was written by Lukas Schollenberger. Yvonne Wagner, Ines Samel and Kristina Probst were affiliated with Cannamedical Pharma GmbH at the time the study was conducted. All authors reviewed and commented the draft manuscript and approved the final manuscript for publication.

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

Declarations

Conflict of Interest. Joachim Nadstawek and Yvonne Wagner received consulting fees from the sponsor Cannamedical Pharma GmbH for scientific and medical consultancy work as advisors and speakers. Ines Samel, Kristina Probst, Lukas Schollenberger and Christian Ruckes have nothing to disclose. Yvonne Wagner is now working as a freelance medical science business consultant at Acantha Lifescience. Ines Samel is currently affiliated with Hormosan Pharma GmbH and Kristina Probst is currently affiliated with AstraZeneca GmbH.

Ethics Approval. The study adhered to the principles of the Declaration of Helsinki of 1964 and its later amendments, the German Medicinal Products Act, the professional code of conduct for physicians, and the GDPR in their respective valid versions. In compliance with the German Medicinal Products Act, the study was notified to the Federal Institute for Drugs and Medical Devices, the National Association of Statutory Health Insurance Physicians, the National Association of Statutory Health Insurance Funds, and the Association of Private Health Insurers. Ethical approval was obtained from the coordinating Ethics Committee at the Medical Association of North Rhine (Application number 2021414) and the local ethics committees involved (list of ethics committees in the supplementary material). The study was registered with the German Clinical Trials Registry (DRKS00026906). All patients gave written informed consent before participating.

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