# Medicinal Cannabis use in patients with chronic pain

## O uso da Cannabis medicinal nos pacientes com dor crônica

## O uso de Canábis medicinal por pacientes com dor crônica

### RESUMO

Objetivo: A dor crônica (DC) possui um impacto significativo na qualidade de vida (QV) da população. Ela repercute na capacidade funcional, podendo influenciar em maiores níveis de dependência, distúrbios do sono, alterações do humor e apetite. A descoberta do sistema endocanabinóide na dor demonstrou melhorar a QV de indivíduos com DC. Esse estudo busca analisar o uso da cannabis medicinal (CM) através da experiência terapêutica de pacientes diagnosticados com dor crônica, observando a interferência na dor, sono, humor e na QV e a ocorrência de efeitos colaterais (EC) Trata-se de um estudo observacional longitudinal, descritivo e prospectivo. A coleta foi realizada através de um formulário digital respondido no início do uso do canabinoide, após primeiro mês e no terceiro mês de uso. Os dados revelaram uma associação entre o uso da CM com a melhora da QV e uma deterioração significativa da dor, humor e do sono. Não houve EC significativos.

**DESCRITORES:** *Cannabis* medicinal; Dor crônica; Tratamento.

### ABSTRACT

Objective: Chronic pain (CD) has a significant impact on the population's quality of life (QoL). It has an impact on functional capacity and can influence higher levels of dependence, sleep disorders, changes in mood and appetite. The discovery of the endocannabinoid system in pain has been shown to improve the QoL of individuals with CD. This study seeks to analyze the use of medicinal cannabis (CM) through the therapeutic experience of patients diagnosed with chronic pain, observing the interference with pain, sleep, mood and QoL and the occurrence of side effects (CE). Its a longitudinal observational, descriptive and prospective. The collection was carried out using a digital form answered at the beginning of use of the cannabinoid, after the first month and in the third month of use. The data revealed an association between the use of CM with improved QoL and a significant deterioration in pain, mood and sleep. There were no significant CEs.

**KEYWORDS:** *Cannabis* medicinal; Chronic pain; Treatment.

### RESUMEN

Objetivo: El dolor crónico (DC) tiene un impacto significativo en la calidad de vida (CdV) de la población. Repercute en la capacidad funcional y puede influir en mayores niveles de dependencia, trastornos del sueño, cambios en el estado de ánimo y en el apetito. Se ha demostrado que el descubrimiento del sistema endocannabinoide en el dolor mejora la CdV de los individuos con EC. Este estudio pretende analizar el uso de cannabis medicinal (CM) a través de la experiencia terapéutica de pacientes diagnosticados de dolor crónico, observando la interferencia con el dolor, el sueño, el estado de ánimo y la CdV y la aparición de efectos secundarios (EC). Se trata de un estudio longitudinal observacional, descriptivo y prospectivo. La recogida se realizó mediante un formulario digital contestado al inicio del uso del cannabinoide, tras el primer mes y en el tercer mes de uso. Los datos revelaron una asociación entre el uso de CM con una mejora de la CdV y un deterioro significativo del dolor, el estado de ánimo y el sueño. No hubo EC significativos.

**PALABRAS CLAVE:** Cannabis medicinal; Dolor crónico; Tratamiento.

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**Luísa Teixeira Silveira**
Tiradentes University, Brazil. ORCID: 0000-0003-1325-3296

**Maria Letícia Carvalho da Cruz Ramos**
Tiradentes University, Brazil. ORCID: 0000-0001-5909-568X

**Alejandra Debbo**
Federal University of Sergipe, Brazil. ORCID: 0000-0002-7743-5921

**Maria Elisa Sobral Vila Nova de Carvalho Vieira**
Tiradentes University, Brazil. ORCID: 0000-0003-1636-7408

**Gabriela Peres de Oliveira krauss**
Tiradentes University, Brazil. ORCID: 0000-0002-2863-9549

**Marina Mendes Teixeira**
Tiradentes University, Brazil. ORCID: 0009-0003-0677-7849

**Maria Steal Carvalho da Cruz Ramos**
Salvador University, Brazil. ORCID: 0000-0003-3269-9357

**Maria Isabelly Alves Pereira Barbosa**
Salvador University, Brazil. ORCID: 0009-0004-6467-4730

## INTRODUCTION

Pain is a difficult to understand and multifactorial condition, defined by the International Association for the Study of Pain (IASP) as an "unpleasant sensory and emotional experience associated with a real injury"[1]. Pain can be triggered by various types of stimuli, such as mechanical, thermal and chemical painful stimuli.

Regarding the temporal subclassification, it can be acute and chronic, with chronic pain (CP) being that which persists after three months beyond the usual healing time of an injury, or which is associated with chronic pathological processes, which cause continuous or recurrent pain [1]. It is estimated that the prevalence of chronic pain in the world is around 10.1 to 55.5%, with an average of 35.5%. According to Aguiar (2021)[1], approximately 60 million people suffer from CD, corresponding to around 10% of the world population. Still on the biological mechanisms accepted by the IASP, CP can be classified as neuropathic, nociplastic and nociceptive. However, regardless of the type of pain experienced, it is a subjective, complex, multidimensional and unpleasant experience.

Chronic pain in general has a significant impact on the population's quality of life. The WHO, through The World Health Organization Quality Of Live Group [3], indicates that: "Quality of life has a multidimensional nature, which includes physical, psychological, social and spiritual dimensions, it encompasses both positive and negative aspects , has a subjective essence." In this way, it is confirmed that chronic pain has a major impact on the individual's quality of life, as well as that of everyone around them. It has repercussions on functional and productive capacity, demonstrated by the reduction in the ability to carry out daily activities such as studying, carrying out domestic tasks and others, which can influence greater levels of dependence. It can also lead to comorbidities such as sleep disorders, anxiety and depression -emotional, psychological and social impact-, changes in mood and appetite [2].

The drug therapy for chronic pain proposed by the World Health Organization (WHO) consists of two protocols: the graduated form includes analgesics, anti-inflammatories, adjuvant drugs and opioids, aiming to act on nociceptive and mixed pain [3], while in the presence of chronic neuropathic pain, it is followed by tricyclic antidepressants and antiepileptics, with opioids being reserved for refractory cases [3,4]. Opioids are excellent analgesics, however, their continuous use presents a high risk of tolerance, requiring increasingly larger doses to achieve an initial analgesic effect and exponentially increasing the risk of adverse effects, chemical dependency and substance abuse [5].

At the beginning of the 90s, the discovery of the endocannabinoid system and its organic effects in modulating pain, especially chronic pain, represented an unknown source of possibilities for the production of medications that, theoretically, would have great potential to improve the quality of life of individuals with chronic pain [1]. With the advancement of research and the insufficiency of treatments for pain relief in patients, in February 2022, 37


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states, three territories, and the District of Columbia allow the medical use of cannabis products in the United States, making it much more widely available [6]. Even with traditional evidence-based studies and legalization as a therapeutic product by legislative bodies in a growing number of countries, the use of cannabis for medical reasons is still contested. According to Finn, 2021 [7], one factor that has hampered the debate about cannabis and cannabinoids for the treatment of pain is the inappropriate and unclear use of terminology. For example, the terms "cannabis," "cannabinoids," and "cannabis-based medicines (CBM)" are often used conflictingly, both in public discourse and media, and in scientific literature [7].

As stated, even knowing the great potential of the plant, to date, the therapeutic use of cannabinoids in the treatment of chronic pain remains controversial due to the limited clinical evidence found in large, randomized clinical studies, the heterogeneity of cannabis-based medicines, and the value of the treatment. Therefore, this study seeks to analyze, in the short and medium term, the use of Medicinal Cannabis through the therapeutic experience of patients diagnosed with chronic pain, so that it is possible to observe the interference with pain, sleep, mood and quality of life. The occurrence of side effects triggered by the use of MC during treatment will also be assessed.

## METHOD

### Study Type

This is a longitudinal observational study, descriptive and prospective.

### Population

Patients diagnosed with any etiology of chronic pain and who are using Medicinal Cannabis, monitored in the office of the rheumatologist and research advisor, in the private office of Centro Médico Jardins in Aracaju-SE.

### Sample

During a period of 3 months, patients diagnosed with chronic pain and who are using Medicinal Cannabis correctly were included. This study presents a convenience sample, as it is not possible to predict the number of patients diagnosed with chronic pain who use MC in private rheumatology practices.

### Risks

The study involves potential risks such as the identification of patient data included in the research, but these will be minimized, as the information obtained will be confidential. None of the information collected will contain the name of the patient involved, but rather a number to make it impossible to identify the patient. Therefore, participants are assured of complete confidentiality, in addition to the guidance that they should only answer the question if they feel comfortable with it.

### Data collection and research instruments

Data collection was carried out through the application of a Google forms digital form, including the SF-36 quality of life questionnaire [8], the analogue pain scale [9] and subjective questions about the patient's type of pain; type of MC and dose in use; use of other pain medications; sleep and mood disorders and fatigue, in addition to sociodemographic data, such as; age, race; marital status and current occupation.

After approval by the CEP, collection began, where the questionnaire was sent to patients who met the inclusion criteria for the study. Patient data were recorded on enumerated forms without identifying them, for subsequent analysis of the collected data.

The form was sent every month, on the same date, until three (3) months of using cannabis oils were completed. As it is longitudinal and aims to monitor the chronic pain of volunteers over a period of 3 months, data collection began with the Initial Form. This was sent before or as soon as patients started using it, and has the Free and Informed Consent Form (FICF); the start date of treatment; patient pain diagnosis; which oil and planned dose to start using; use of other associated medications; presence or absence of insomnia, fatigue and mood disorder and, the SF-36 questionnaire [8] and the pain scale [9].

In months one (1) and three (3) of medication use, the Monitoring Forms are applied, containing similar questions, but with questions that assess whether or not to maintain the oil/dose, co-medication, the improvement or not of sleep, fatigue and mood, as well as the emergence of possible side effects such as drowsiness, nausea, dry mouth, among others.

### Ethical considerations

This research was submitted to the Research Ethics Committee of Universidade Tiradentes (UNIT). Approved, under CAAE Number: 61304622.0.0000.5371. The entire studied population signed the free and informed consent form (FICF), guaranteeing the interviewees, according to resolution 466/12, anonymity and the possibility of withdrawing their consent at any time without prejudice.

### Data Analysis

Exploratory data analysis was carried out with simple frequency and percentage calculations. In the longitudinal analysis, the McNemar (1952) and Stuart-Maxwell (10,11) tests were used for the analysis of qualitative variables, and the Friedman (1937) test (12) with the Conover (1979) post-hoc test (13) for the pain scale and the quality of life scale. The Cross-sectional analysis used Fisher's Exact test (10) to associate the presence of THC with other qualitative variables, and the results were expressed in terms of frequency and percentage calculated depending on the column. In the relationship be-

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tween pain scale scores and quality of life, the cross-sectional analysis used the Mann-Whitney test (1947) (14), and the results were expressed in terms of mean and standard deviation. Adherence to the Normal distribution was assessed using the Shapiro-Wilks test (1965) (15). The data were organized in the Microsoft Excel program, and all statistical analyzes were performed in the R software, version 4.2.3 (16). The significance level adopted throughout the work is 5%.

## INCLUSION CRITERIA:

The study included adults aged 18 and over, with one or more chronic pain conditions (three months of pain), who were starting cannabis-based medications and using them for at least a period of 3 months, orally and at any dose.

## EXCLUSION CRITERIA:

-Patients who discontinued the use of the drug during the study period, regardless of the cause.
-Former cannabis users.
-Incomplete filling out of forms

## RESULTS

The final study sample consisted of 21 volunteers. Of these, 61.9% (N=13) are adults, under the age of sixty, and 38.1% (N=8) are elderly. The predominant race/color was black/brown with 71.4% (N=15), followed by whites 28.57% (N=6). 57% of people are married or have a stable union and 42.86% are single. Of the 21 patients, 13 have some type of paid activity. Regarding the diagnosis of pain, a large part of the sample, 52.38%, has Fibromyalgia (N=11), followed by osteoarthritis (N=8; 38.1%). Furthermore, diagnoses such as: undifferentiated arthritis (N=5), discopathy (N=2), neck pain and others were found. Twelve volunteers have only 1 type of pain, while eight of them have 2 pain diagnoses and only one of them has 4 diagnoses. Most patients have insomnia (N=16; 76.19%), frequent fatigue (N=17; 80.95%) and some mood disorder (N=20; 95.24%), anxiety disorder being predominant (85%), followed by depressive disorder and panic syndrome with 45% and 10%, respectively (Table 1).

Regarding the type of cannabis oil used by study volunteers, oil rich in CBD was predominant throughout the follow-up period, with 13 patients (61.9%) using it at the beginning of treatment, 14 (66.7) after one month of treatment and in the last month, returning to N=13 (61.9%). The least used type of oil was the balanced CBD:THC, with only 2 patients (9.5%) in the questionnaires for the first and

**Table 1: Absolute and relative frequency (%) of the characteristics of study participants, Aracaju, Sergipe, Brazil**

| Variable/Category | Frequency | Percentage |
|---|---|---|
| **AGE GROUP** | | |
| Adult | 13 | 61,90 |
| Elder | 8 | 38,10 |
| **RACE** | | |
| WHITE | 6 | 28,57 |
| BLACK/BROWN | 15 | 71,43 |
| **Marital Status (Stable Union)** | | |
| Yes | 12 | 57,14 |
| No | 9 | 42,86 |
| **PAID ACTIVITY** | | |
| NO | 8 | 38,10 |
| YES | 13 | 61,90 |
| **PAIN DIAGNOSIS** | | |
| FIBROMYALGIA | 11 | 52,38 |
| ARTHROSIS | 8 | 38,10 |
| ARTHRITIS | 5 | 23,81 |
| CERVICALGIA | 1 | 4,76 |
| DISC HERNIATION | 2 | 9,52 |


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| | | |
|---|---|---|
| MYOFASCIAL SYNDROME | 1 | 4,76 |
| HIP BURSITIS | 1 | 4,76 |
| CARPAL TUNNEL SYNDROME | 1 | 4,76 |
| EHLERS-DANLOS SYNDROME | 1 | 4,76 |
| BACKACHE | 1 | 4,76 |
| **Total of Pains** | | |
| 1 | 12 | 57,14 |
| 2 | 8 | 38,10 |
| 4 | 1 | 4,76 |
| **Has Insomnia?** | | |
| NO | 5 | 23,81 |
| YES | 16 | 76,19 |
| **Does the person feel tired (fatigue) frequently?** | | |
| NO | 4 | 19,05 |
| YES | 17 | 80,95 |
| **Does the person have a mood disorder?** | | |
| NO | 1 | 4,76 |
| YES | 20 | 95,24 |
| **Which mood disorder?** | | |
| Anxiety | 17 | 85,00 |
| Depression | 9 | 45,00 |
| Panic Syndrome | 2 | 10,00 |

third month of using the substance. The study showed that most patients use other medications to treat chronic pain, with a decrease in these drugs in the last month of follow-up, N=17 (81.0%), N=18 (85.7%) and N=13 (61.9%), respectively.

In months 1 and 3 of treatment, the perception of improvement in sleep, pain and mood disorders, as well as the occurrence of possible side effects, were assessed. Of the total sample, 72.2% observed improved sleep after three months of using the drug, while 4 of them did not notice improved sleep after this period. Of the 21 volunteers, 13 patients noticed an improvement in pain in the first month of using the medication and 15 of them after the end of the three months. Regarding users who have a mood disorder, N=13 (61.9%) remained during months of follow-up 1 and 3.

Related to the presence of side effects, the main ones evaluated were drowsiness, nausea, dizziness, palpitation, headache, blurred vision, dry mouth, diarrhea and tiredness. (Table 2).

Comparing follow-up 1 with 2, of the patients who showed improvement in pain in the first month of use, 84.6% also noticed an improvement in follow-up 2 (Table 3). Making the same comparison, but now in relation to side effects, the main ones observed were drowsiness and dry mouth, with 87.5% and 88.9%, respectively, without the need to discontinue the medication.

Regarding improvement in sleep and mood disorders, of the volunteers who observed improvement in the first month of use, 92.9% also noticed it after the third month. And of those who improved their mood disorders, 11 of them (84.6%) continued with a positive outcome after ninety days of using medicinal cannabis (Table 4).

In Table 5, we present the results of the Visual Analogue Pain Scale (VAS), in which the number 10 represents the worst possible pain, together with the aspects of the Quality of Life Questionnaire (SF-36), where scores closer to one hundred (100) indicate a better quality of life. The study compared patients' pain at the beginning of using the medication, with an average of 7.9 (SD=1.8), during month one, 6.4, and at the end of the third month, with an average of 6.0, achieving significant relevance between the periods.

Regarding aspects of quality of life, in addition to pain, functional capacity, physical, social and emotional aspects, general health, vitality and mental health were observed.

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**Table 2: Absolute and relative frequency (%) of study variables**

| Variable/Category | Initial (%) | Follow-up 1 (%) | Follow-up 2 (%) |
|---|---|---|---|
| **Cannabis oil that you use** | | | |
| BALANCED CBD:THC | 1 (4.8) | 2 (9.5) | 2 (9.5) |
| RICH IN CBD | 13 (61.9) | 14 (66.7) | 13 (61.9) |
| COMBINED | 3 (14.3) | 4 (19.0) | 5 (23.8) |
| ISOLATED | 4 (19.0) | 1 (4.8) | 1 (4.8) |
| **Use of other pain medications** | | | |
| NO | 4 (19,0) | 3 (14,3) | 8 (38,1) |
| YES | 17 (81,0) | 18 (85,7) | 13 (61,9) |
| **Noticed improvement in sleep** | | | |
| I DIDN'T NOTICE AN IMPROVEMENT IN SLEEP | | 4 (19,0) | 4 (19,0) |
| NO, MY SLEEP HAS NOT IMPROVED | | 3 (14,3) | 1 (4,8) |
| YES, MY SLEEP HAS IMPROVED | | 14 (66,7) | 16 (76,2) |
| **Noticed improvement in pain** | | | |
| NO | | 8 (38,1) | 6 (28,6) |
| YES | | 13 (61,9) | 15 (71,4) |
| **Noticed improvement in mood disorder** | | | |
| NO | | 5 (23,8) | 4 (19,0) |
| I DON'T HAVE A MOOD DISORDER | | 3 (14,3) | 4 (19,0) |
| YES | | 13 (61,9) | 13 (61,9) |
| **Occurrence of Drowsiness** | | | |
| NO | | 13 (61,9) | 12 (57,1) |
| YES | | 8 (38,1) | 9 (42,9) |
| **Occurrence of Nausea** | | | |
| NO | | 15 (71,4) | 19 (90,5) |
| YES | | 6 (28,6) | 2 (9,5) |
| **Occurrence of Dizziness** | | | |
| NO | | 14 (66,7) | 16 (76,2) |
| YES | | 7 (33,3) | 5 (23,8) |
| **Occurrence of Palpitation** | | | |
| NO | | 15 (71,4) | 18 (85,7) |
| YES | | 6 (28,6) | 3 (14,3) |
| **Occurrence of Headache** | | | |
| NO | | 17 (81,0) | 18 (85,7) |
| YES | | 4 (19,0) | 3 (14,3) |
| **Occurrence of Blurred Vision** | | | |
| NO | | 15 (71,4) | 17 (81,0) |
| YES | | 6 (28,6) | 4 (19,0) |


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| | | |
|---|---|---|
| Occurrence of Dry Mouth | | |
| NO | 12 (57,1) | 12 (57,1) |
| YES | 9 (42,9) | 9 (42,9) |
| Occurrence of Diarrhea | | |
| NO | 19 (90,5) | 21 (100,0) |
| YES | 2 (9,5) | 0 (0,0) |
| Occurrence of Tiredness | | |
| NO | 17 (81,0) | 15 (71,4) |
| YES | 4 (19,0) | 6 (28,6) |

Caption: Initial: responses referring to the initial questionnaire; Follow-up 1: responses referring to follow-up questionnaire 1, after 1 month of drug use; Follow-up 2: responses referring to follow-up questionnaire 2, with 3 months of drug use

**Table 3: Crossover between follow-up 1 and follow-up 2 based on pain improvement and side effects**

| Follow-up 1 | Follow-up 2 | | P |
|---|---|---|---|
| | NO (%) | YES (%) | |
| **Pain improvement?** | | | |
| NO | 4 (50,0) | 4 (50,0) | 0,683 |
| YES | 2 (15,4) | 11 (84,6) | |
| **Drowsiness** | | | |
| NO | 11 (84,6) | 2 (15,4) | 1,000 |
| YES | 1 (12,5) | 7 (87,5) | |
| **Nausea** | | | |
| NO | 15 (100,0) | 0 (0,0) | 0,134 |
| YES | 4 (66,7) | 2 (33,3) | |
| **Dizziness** | | | |
| NO | 12 (85,7) | 2 (14,3) | 0,683 |
| YES | 4 (57,1) | 3 (42,9) | |
| **Palpitation** | | | |
| NO | 15 (100,0) | 0 (0,0) | 0,248 |
| YES | 3 (50,0) | 3 (50,0) | |

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| | | | |
|---|---|---|---|
| **Headache** | | | |
| NO | 16 (94,1) | 1 (5,9) | 1,000 |
| YES | 2 (50,0) | 2 (50,0) | |
| **Blurred vision** | | | |
| NO | 11 (73,3) | 4 (26,7) | 0,752 |
| YES | 6 (100,0) | 0 (0,0) | |
| **Dry Mouth** | | | |
| NO | 11 (91,7) | 1 (8,3) | 1,000 |
| YES | 1 (11,1) | 8 (88,9) | |
| **Diarrhea** | | | |
| NO | 19 (100,0) | 0 (0,0) | 0,480 |
| YES | 2 (100,0) | 0 (0,0) | |
| **Tiredness** | | | |
| NO | 13 (76,5) | 4 (23,5) | 0,683 |
| YES | 2 (50,0) | 2 (50,0) | |

Caption: Follow-up 1: responses referring to follow-up questionnaire 1, with 1 month of drug use. Follow-up 2: responses referring to the follow-up questionnaire 2, with 3 months of drug use

**Table 4: Comparison between follow-up 1 and 2 regarding improvement in sleep and mood disorder**

| Follow-up 1 | Follow-up 2 | | | p |
|---|---|---|---|---|
| | I DIDN'T NOTICE AN IMPROVEMENT (%) | NOT IMPROVED (%) | YES (%) | |
| **Sleep improvement** | | | | |
| I DIDN'T NOTICE AN IMPROVEMENT | **1 (25,0)** | **1 (25,0)** | **2 (50,0)** | **0,449** |
| NOT IMPROVED | **2 (66,7)** | **0 (0,0)** | **1 (33,3)** | |
| YES | **1 (7,1)** | **0 (0,0)** | **13 (92,9)** | |
| **Improvement of mood disorder** | **NO (%)** | **NO TENHO TRANSTORNO (%)** | **YES (%)** | |
| NO | **3 (60,0)** | **1 (20,0)** | **1 (20,0)** | **0,834** |
| I DON'T HAVE A DISORDER | **1 (33,3)** | **1 (33,3)** | **1 (33,3)** | |
| YES | **0 (0,0)** | **2 (15,4)** | **11 (84,6)** | |

Caption: Follow-up 1: responses referring to follow-up questionnaire 1, with 1 month of drug use. Follow-up 2: responses referring to the follow-up questionnaire 2, with 3 months of drug use.


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**Functional capacity:**

At the beginning of use, there was a worse functional capacity, with an average of 29. During months 1 and 3, there was a significant improvement in functional capacity, with averages of 40.7 and 43.8, respectively. This indicates that the treatment had a positive impact on functional capacity over time.

**Physical aspects:**

The physical appearance was worse during the beginning of treatment. In the 1st month of use, the physical appearance had not yet improved significantly compared to the beginning of treatment. In the 3rd month of use, there was a significant improvement in physical aspects.

**General Health Status:**

At the beginning of treatment, the general health condition was worse. In the 1st month of use, there was an improvement in the quality of general health. In the 3rd month of use, the general health status remained similar to that observed in the 1st month.

**Vitality:**

At the beginning of use, the vitality was worse. In the 1st month of use, there was an improvement in vitality. In the 3rd month of use, vitality was similar to that observed in the 1st month.

**Social aspects:**

Social aspects followed a similar pattern to physical aspects, with a significant improvement during the 3rd month of use compared to the beginning of treatment. In the 1st month of use, social aspects had not yet improved significantly compared to the beginning of treatment.

**Emotional Aspects and Mental Health:**

It was not mentioned whether there were statistically significant changes in emotional aspects and mental health throughout the treatment. Therefore, these aspects may not have been affected by the treatment or were not assessed in a relevant way (Table 5).

## DISCUSSION

Cannabis is a plant used for pharmacological effects. There are over 500 chemicals found in the plant. Two main subspecies are cannabis indica and cannabis sativa [17]. The Cannabis sativa plant contains more than 100 different cannabinoids – the most abundant are the main psychoactive components, Δ 9 -tetrahydrocannabinol (THC), and cannabidiol (CBD) [18].

The understanding of the endocannabinoid system is continually expanding and studied, however, in essence it can be defined by three main components: the ligands (endocannabinoids), the receptors for these ligands (cannabinoid receptors), and the enzymes responsible for the synthesis and degradation of these ligands [20]. Cannabinoids can be categorized into three types: phytocannabinoids, endocannabinoids and synthetic cannabinoids.

Phytocannabinoids are exogenous cannabinoids, not found in the human body, isolated from the cannabis plant; and, when ingested, they bind to cannabinoid receptors (CB1 and CB2). CBD is a non-psychoactive phytocannabinoid found in approximately 40% of cannabis extracts and has analgesic and anti-inflammatory properties. As such, CBD provides analgesic properties through the anti-inflammatory pathways of these receptors without causing a psychotropic effect [21]. Studies show improvements in the use of THC-containing CBMPs, particularly in patients with neuropathic pain. It is therefore intriguing that several experts have supported the choice of predominantly CBD to begin treating patients with chronic pain, an approach aimed at promoting safety over efficacy, considering that side effects observed with medical cannabis are primarily attributable to THC (e.g., drowsiness, dizziness) and clinical evidence of CBD's analgesic potential is minimal [22].

Endocannabinoids are endogenous cannabinoids found in the human body. There are two types: anandamide and 2-arachidonoylglycerol (2-AG). The mechanism of action by which these substances exert their effects involves binding to G protein-coupled CB1 and CB2 receptors throughout the body, stimulating the endogenous cannabinoid system, altering the levels of endocannabinoids (eCBs) and inhibiting the release of neurotransmitters such as gamma-aminobutyric acid (GABA) and glutamate [23]. CB1 receptors are found in the brain and periphery (e.g., intestines, liver, fat and immune cells) [24]. These receptors are remarkably similar in neurochemical structure to opioid receptors and are believed to modulate nociceptive processing in the brain [25]. On the other hand, CB2 receptor expression in CNS neurons is lower compared to CB1; and is expressed to a much greater extent in glial cells of the CNS, in areas that are known sites of intense nociceptive integration, and of the PNS and throughout the immune system [24]. CB2 receptors that are involved in the release of analgesic beta-endorphins have been shown to reduce C-fiber activity in models of neuropathic pain. CB1 and CB2 receptors also allow for other forms of neuromodulation, including increased dopamine release, decreased acetylcholine release, and decreased norepinephrine release. eCBs are endogenous neuroactive lipid messengers that play a role in reward, memory, learning, and pain pathways. Therefore, the endocannabinoid system has become a potential target site for future pain intervention strategies [23].

Synthetic cannabinoids are sold over the counter or by prescription, considered illegal and banned by the federal government in many states. These bind to cannabinoid receptors, but can affect the brain in unpredictable ways compared to THC. The Federal Drug Administration (FDA) has only approved synthetic cannabinoids containing

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delta-9-THC analogues for prescriptions. These synthetic cannabinoids are Dronabinol (Marinol®, Syndros®) and nabilone (Cesamet®) and are indicated for nausea and vomiting and appetite stimulation, but are also often used off-label for pain management [17].

Although many medical cannabis products are THC dominant, the products may contain THC-free CBD, CBD with small amounts of THC (e.g., 10:1 CBD:THC ratio) or substantial amounts of THC (e.g., 1:1 CBD:THC). Formulations include (1) isolates (CBD only), (2) "full spectrum" with minor cannabinoids and plant components such as terpenes and flavonoids, and (3) enriched products containing additives such as cinnamon, cloves, arnica, or turmeric [25].

Overuse of prescription opioid medications such as morphine and codeine has contributed to the opioid crisis, indicating the need for new pharmacologic and nonpharmacologic treatment options for chronic pain to reduce abuse of prescription opioid medications. Thus, cannabis-based medicines began to be widespread and prescribed in different chronic pain conditions [26].

**Sociodemographic conditions: Sex, age and race**

The diagnosis of chronic pain is higher in females compared to males. Clinically, it has been reported that women are more sensitive and less tolerant to experimental pain than men (20). Although there is not enough information about the mechanisms, there is some evidence for the role of estrogens and genetics. In the study in question, out of N=21, 20 were women with different pain diagnoses and only 1 of them was male. Of these patients, 61.9% were adults up to 59 years old and the other 38.1% were over 60 years old. According to MILLS, 2019, advanced age and chronic pain have a complex interrelationship, whereby multimorbidity is independently associated with chronic pain [27]. However, many diagnoses of chronic pain, such as fibromyalgia and different types of arthritis, are present in middle-aged patients. The highest prevalence of fibromyalgia was found in the age group of 55 to 65 years (1.05% in 2010 and 2.46% in 2017) [28].

Related to race, 71.43% of the patients in this study are black or mixed race. Corroborating reviews showing that Caucasians experience less pain and less pain-related disability than black patients [27].

**Pain etiologies**

Patients who suffer from chronic pain may have different types of diagnoses - including more than one of them - as various musculoskeletal, neurological, degenerative, autoimmune diseases, among others, can be the initial cause. In addition to the sequelae of cancer and musculoskeletal diseases, which are very prevalent. In the present study, fibromyalgia corresponding to 52.38% and osteoarthritis, 38.1%, are diseases that affect many areas related to quality of life, such as sleep, mood and decreased functional capacity. These diseases have chronic pain as their main symptom. Patients who suffer from these pathologies may also have other associated diagnoses, as occurred in this study with 38.1% of volunteers who had two diagnoses.

**Improved pain and quality of life**

Related to the improvement in pain with the use of cannabis, of the 21 volunteers, 13 patients noticed an improvement in pain in the first month of using the medication and 15 of them after the end of the three months. The study also compared patients' pain at the beginning of using the medication, with an average of 7.9 (SD=1.8); during the first month, being 6.4, and at the end of the third month, with an average of 6.0, obtaining significant relevance between the periods. In a review of 16 studies involving a total of 1750 people, comparing medical cannabis and placebo, cannabis-based medicines were superior to placebo in reducing average pain intensity. Regarding aspects of quality of life, in addition to pain, functional capacity, physical, social and emotional aspects, general health, vitality and mental health were observed.

**Types of oils**

In this study, some types of oils were used by the patients approached, among those used were: Full spectrum cannabis oil, CBD:THC balanced oil; Oil rich in full spectrum CBD and isolated CBD Oil. Regarding the type of cannabis oil most used by study volunteers, the oil rich in full spectrum CBD was predominant throughout the follow-up period, with 13 patients (61.9%) using it at the beginning of treatment, 14 (66 .7%) after one month of treatment and in the last month, it returned to N=13 (61.9%). The least used type of oil was the balanced CBD:THC, with only 2 patients (9.5%) in the questionnaires for the first and third month of using the substance. CBD is well tolerated even at very high doses, up to 6,000 mg, and has relatively benign side effects, the most common being diarrhea. Other side effects such as drowsiness, decreased appetite and fatigue are evident especially when other medications are co-administered. Additionally, THC has well-documented side effects, including dizziness, appetite stimulation, drowsiness, mood swings, anxiety, and impaired cognition and attention. These effects vary according to the dose and route of administration, and rapid tolerance to such effects may occur. This corroborates this study, as THC has proven to have more side effects and is less tolerated by patients, oils based solely on CBD end up being more updated in general [29].

**Side Effects**

The main side effects associated with the use of medicinal Cannabis are: drowsiness, dizziness, nausea, dry mouth, palpitation, blurred vision, diarrhea and tiredness. In this study, comparing follow-up 1 with 2, in relation to


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side effects, the main ones observed were drowsiness and dry mouth, with 87.5% and 88.9%, respectively, without the need to discontinue the medication. This reinforces the literature that shows evidence from randomized clinical trials an association with drowsiness and cannabidiol and cannabis-based medications and dizziness, sedation and vertigo [26].

**Co-medication**

In the study in question, at the beginning of treatment, 17 (81%) patients were using other medications. In the first month's follow-up questionnaire, 18 (85.7%) patients were using other medications, finally, in the third month follow-up questionnaire, 13 (61.9%) patients were using medications associated with cannabidiol. It is notable that initially patients had a greater need for co-medication, as in the first month of using the oil there is a period of adaptation to the medication, with periodic dose adjustments, with the therapeutic effect depending on each patient. Therefore, during this period there may be a greater need for other medications to relieve pain, which with the passage of time and adaptation to the cannabinoid, this need tends to decrease. In the last follow-up, after 3 months of using medicinal cannabis, a decrease in the need to use other medications associated with it is visible. Compared to the Literature, in a prospective cohort study by Capano et al., with 97 participants on the effect of CBD hemp extract on chronic pain patients taking opioid medication, the primary outcome showed that by the eighth week of use, 50 of 94 (53.2%) had tapered off their opioid medications. The secondary outcome reported that 89 (94%) improved quality of life as measured by pain and open-ended questions related to sleep [30]. Furthermore, studies have concluded that CBD is effective in reducing the stress response and its manifestations of fear, anxiety, depressive behaviors or exhaustion. Two of these studies included benzodiazepines, and both concluded that CBD is superior to the efficacy of the pharmaceutical drug [31]. This corroborates the results of the study in question.

**Sleep and mood disorder**

Cannabis-based medications were superior to placebo in reducing sleep problems and statistically significantly better in reducing psychological distress. This confirms the study in question, as in months one [1] and three [3] of treatment, the perception of improvement in sleep, pain and mood disorders were evaluated, as well as the occurrence of possible side effects. Of the total sample, 72.2% observed improved sleep after three months of using the drug, while 4 of them did not notice improved sleep after this period. Another study showed that among 15 individuals with insomnia, results suggested that administering 160 mg/day of CBD increased total sleep time and decreased the frequency of awakenings during the night, but with drowsiness reported by some, in a retrospective case series that examined the effect of CBD on 72 adults for anxiety and sleep, anxiety scores decreased within 1 month in 57 (79%) and remained reduced. In a systematic review of 6 randomized clinical trials, 1 case series, and 1 case report, Skelley et al. reported that CBD at doses of 6–400 mg per dose appeared to consistently improve anxiety and was well tolerated [24]. In the results of this study in question, 13 patients (61.9%) in the first month's follow-up achieved improvement in their mood disorder, maintaining this number in the third month's follow-up, confirming Boehnke, 2022 [24].

**Different types of oils**

In this study, all types of oils prescribed for the treatment of chronic pain were used, such as cannabis oils rich in cannabidiol, as well as associations of different dosages of CBD with THC. The vast majority of patients used CBD-rich oils from the beginning to the end of the follow-up period. Delta-9-tetrahydrocannabinol (THC) is the main psychoactive compound in cannabis and exerts its psychoactive and analgesic effects mainly through its partial agonist activity at endogenous cannabinoid receptors (endocannabinoids), cannabinoid receptors type 1 (CB 1) and type 2 (CB2). High-quality evidence of efficacy is best for combined THC/CBD medications for chronic pain and CBD-only medications for stress and anxiety. Additionally, THC is generally not appropriate for chronic insomnia due to habituation of any short-term benefits it provides, reports of worsening sleep onset latency, and daytime sleepiness from THC [31].

## CONCLUSION

It is known that chronic pain is the cause or consequence of several other stressful factors, such as sleep disorders, mood disorders and decreased quality of life as a whole. Therefore, interest in the use of medicinal cannabis to treat pain was reinforced by the challenges of treating pain in adults with minimal potential for adverse effects. Several pillars are still needed for greater dissemination of the medication, but its effectiveness in improving chronic pain and the general quality of life of users is relevant. There are now different oils available for treatment. The vast majority of adverse effects are mild to moderate, the main ones being drowsiness and dry mouth, without the need to discontinue the substance.

The use of cannabis oils is capable of reducing dependence on opioid and benzodiazepine medications in the population with chronic pain.

More future studies are needed, preferably experimental, with standardization of oils, doses, with longer duration and comparison between the effects of CBD x THC, to better determine the results.

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