Clinical Trial

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Medical Cannabis in Patients with Chronic Pain: Effect on Pain-Relief, Pain Disability, and Psychological aspects. A Prospective Non randomized Single Arm Clinical Trial

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Abstract

There is an increasing interest in the medical use of cannabis, particularly in the treatment of chronic pain.

Objectives. The aim is to evaluate the effects of cannabis use and the associated benefits reported by patients with various chronic pain diagnoses.

Materials and methods. A total of 338 patients with different chronic pain conditions were treated with a Cannabis Flos 19% decoction for 12 months, in addition to their pharmacological therapy. Baseline levels for pain medications, pain intensity, pain disability, anxiety and depression were recorded at 1, 3, 6 and 12 months.

Results. Pain intensity records a statistically significant reduction from Baseline to 12 months follow up (X^2 61.375; P< 0,001); the improvements from Baseline to 12 months follow up are also recorded in pain disability (X^2 39.423; P<0,001) and in anxiety and depression symptoms ($X^2$30.362; P<0,001; $X^2$27.786; P<0,001).

Conclusions. Our study suggest that Cannabis therapy, as an adjunct a traditional analgesic therapy, can be an efficacious tool to make more effective the management of chronic pain and its consequences on functional and psychological dimension. Further randomized, controlled trials are needed to confirm our conclusions. ***Clin Ter 2018; 169(3):e102-107. doi: 10.7417/CT.2018.2062***

Key words: *Anxiety, Chronic Pain, Depression, Medical Cannabis, Pain Disability*

Introduction

Chronic pain is a common condition difficult to treat in the field of pain management. One in five adults in Europe (75 million of people) suffers from moderate to severe pain (1) On average, 38% of European patients with chronic pain reported that their condition is not adequately managed (2) Moreover, chronic pain may have a significant impact on quality of life: the report "The Painful Truth" shows that more than a third of people with chronic pain found difficulties to carry out everyday activities (3-4). Many patients develop depression, anxiety or sleep disorders. The feeling of isolation and the belief that pain has become the focus of the patient's life are also frequent (5). The Painful Truth Survey findings reveal that less than half of survey respondents feel they have had a good experience with conventional medication. The results also reveal that a third have tried three or more prescribed treatments for their chronic pain, yet more than half experience pain relief only for 1-2 days per week and 68% of respondents still in pain for 12 hours or more a day, despite treatment. Moreover, the evidence is not fully convincing for most complementary and alternative medicine modalities (4). For many centuries the cannabis plant (*Cannabis sativa* L.) has been used for various medical problems. According to the increased knowledge of the endocannabinoid system, the preclinical work and the results from different animal models, cannabinoid agonists could be analgesic (6-7). These findings highlight the potential role of cannabis in pain management and preliminary evidence from clinical studies supports this data (8-10) Moreover, recently several meta-analysis and systematic reviews tried to make the point on this issue, showing that there was at least moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain (11).

The most recent of these publication is that of National Academies of Sciences which assessed "there is substantial evidence that cannabis is an effective treatment for chronic pain in adults" (12). Pain syndromes with a positive response to cannabinergic therapies include chronic neuropathic pain, some kind of cancer pain, spasticity, acute pain and chronic pain conditions (13-17). Moreover, there is a growing body of evidence to support the use of medical cannabis as an adjunct to or substitute for prescription opiates in the treatment of chronic pain. When used in conjunction with opiates, cannabinoids lead to a greater cumulative relief of pain, resulting in a reduction in the use of opiates (and associated side-effects) by patients in a clinical setting. Additionally, cannabinoids can prevent the development of tolerance to and withdrawal from opiates, and can even rekindle opiate analgesia after a prior dosage has become ineffective. Novel research suggests that cannabis may be useful in the treatment of problematic substance use. These findings suggest

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that increasing safe access to medical cannabis may reduce the personal and social harms associated with addiction, particularly in relation to the growing problematic use of pharmaceutical opiates (18).

Based on the literature, we wanted to investigate the patterns of medical cannabis use and the associated effects reported by patients with different diagnosis of chronic pain, using medical grade plants of cannabis, produced according to Good Manufacturing Practice, as a therapy in addition to first/second line analgesic drugs.

We specifically examined:

- The efficacy of cannabis in relieving pain;
- Adverse effects.
- The effect of cannabis on pain disability
- The effect of cannabis on anxiety and depression

Materials and methods

The inclusion criteria for eligible patients were:

1) 18 years of age or older;

2) chronic pain for at least 3 months;

3) lack or inadequate response to conventional treatments or presence of adverse effects defined as deemed intolerable effects by patients, who refused to continue the therapy (according to the World Health Organization analgesic ladder).

The exclusion criteria were:

1) pregnant or breast-feeding patients;

2) patients with severe ischemic heart disease or arhythmia;

3) patients with severe psychiatric or personality disorders, a history of cannabis or other psychoactive substances abuse or dependence: for this purpose all patients were psychologically screened prior the study selection with a clinical interview and with the compilation of the M.I.N.I. International Neuropsychiatric Interview.

Study design

A prospective non-randomized single-arm clinical trial study with 1-year follow-up was conducted in the Pain Therapy Unit of Santa Chiara University Hospital of Pisa, between November 2013 and September 2015. Patients with a disease characterized by chronic pain for at least three months, considered eligible on the basis of inclusion and exclusion criteria, were enrolled in the study after their informed consent.

After the first visit in which they have had the diagnosis and the prescription of medical cannabis, the study design provided, in absence of problems, follow-up visits at 1 month,3 months, 6 months and 1 year.

Procedures were in accordance with the ethical standards of the responsible committe on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Therapy

The used drug was the dried flower tops of the cannabis plant. Its THC (tetrahydrocannabinol) level is standardized at 19%, with a CBD (cannabidiol) level below 1%. The used strain was Bedrocan® medicinal cannabis, which are made available by the Dutch Ministry of Health, therefore it is imported from the Netherlands. Cannabis was administered as a decoction. The starting dose was 5 mg/day of THC, corresponding to 28 mg of Cannabis Flos 19%. At the first visit, the patients were asked to sign an informed consent form, wherein they were provided informations related to therapeutic cannabis (explanation of the drug, therapeutic informations, possible acute and long term side effects, mode of consumption, effects on driving and possible interaction with other drugs). The patients were also instructed by the medical staff regarding the preparation of cannabis. The method used was the one recommended by the Office of Medical Cannabis of the Dutch Ministry of Health (https://www.cannabisbureau.nl/), modified according to the analysis carried out at the Laboratory of Clinical Toxicology and Antidoping LAD of the Tuscany Region, which have shown a better extraction with the addition of lipid liquid such as milk (titration THC = 5% by simple infusion, 20% decoction in 15 minutes, 80% by decoction in 15 minutes in water + 5 minutes with whole milk added). In fact, dietary fats and pharmaceutical lipid excipients increase systemic exposure to orally administered cannabis and cannabis-based medicines (19). Co-administration of dietary lipids or pharmaceutical lipid excipients has the potential to substantially increase the exposure to orally administered cannabis and cannabis-based medicines. The cannabis bloom was to be prepared as herbal tea and needed to be heated to over 90 degrees to release its active ingredient. The prescribed preparation method was to boil 200 ml of water in a saucepan with lid, then to add the therapeutic cannabis in the prescribed quantity in a filter, to add 30 ml of milk (THC is fat soluble) and to simmer for 20 minutes. The study protocol was approved by Local Health Care Authority institutional review board.

After approximately 6 months of therapy, most of the patients took a 10-mg dose of THC they maintained their previous pharmacologic therapy, and no one started to take additional conventional medication during the study and no complementary therapeutic approaches had been applied.

Questionnaire Details

To evaluate the effectiveness of cannabis and explore the different aspects of pain, the patients were subjected to a specifics questionnaires. The aim of the questionnaires was to evaluate

Psychopathology;
Pain intensity;
Ability to perform normal daily activities;
Mood and anxiety symptoms.

Psychopathology: The M.I.N.I. International Neuropsychiatric Interview (20) is a short, structured diagnostic interview developed by psychiatrists and clinicians in the United States and Europe for DSM-IV and ICD-10 psychiatric disorders. It is administered for psychiatric evaluation and outcome tracking in clinical psychopharmacology trials end epidemiological studies.

Pain intensity: During the first examination, using the

visual-analogic scale (VAS), the patients were asked to choose their pain level from "no pain" (0 value) to "worst imaginable pain" (10 value).

Pain Disability Index (PDI): The PDI is a tool designed to help patients measure the degree to which their daily lives are disrupted by chronic pain (21) It is composed by seven rating scales, structured in Likert form, from "no disability" (0) to "worst disability" (10) For each of the 7 categories of life activities listed, the patients were asked to circle the number on the scale that described the level of disability typically experienced.

Hospital Anxiety and Depression Scale (HADS): The HADS (22-23) is a self-assessment scale developed to detect states of depression, anxiety and emotional distress among patients. It is composed by a fourteen items: seven of them relate to anxiety and seven relate to depression.

All questionnaires (VAS, PDI, HADS) were repeated, with telephone interviews, 1 month, 3 months, 6 months and 1 year after the onset of therapy and were used as outcome measures.

Statistical methods

The statistical statistical analyzes were conducted with IBM SPSS Statystics Package Version N. 23.

A preliminary study of distribution with Shapiro-Wilk test showed that scores were not normally distributed. So, non-parametric Friedman's test was used to evaluated differences between follow-up for each variables (Pain Intensity, Pain Disability) for baseline, one month and three months after baseline; while, non-parametric Wilcoxon's test was used for variables anxiety and depression, because these symptoms were evaluated not before of three months after baseline; so, in this case we had only two evaluations (baseline and three months after baseline). Graphics show median values because we used non-parametric tests for the statistical analysis.

Confidence interval is at 95%.

Results

Our sample was composed by 338 patients (66% women and 34% men) with an average age of 60.9 ± 14 years old (21-94 years old), affected by fibromyalgia, radiculopathy, headache, arthritis, various form of neuropathic pain and other conditions characterized by chronic pain (Tab. 1; Fig. 1).

Table 1. Descriptive statistic and Clinic Variables at Baseline and Follow up

Age	60 (Xm)	14 (Ds)
Sex (M)	34%	
Sex (F)	66%	
	Median	**Range (Min-Max)**
VAS BL	8,63	2-10
VAS 1	6,56	0-10
VAS 3	6,11	0-10
VAS 6	5,33	0-10
VAS 12	5,37	0-10
ANX BL	8,85	5-20
ANX 3	5,52	7-20
ANX 6	5,56	7-20
ANX 12	5,81	7-20
DEP BL	10,3	5-21
DEP 3	7,04	5-21
DEP 6	6,19	5-20
DEP 12	6,7	5-20
PDI BL	6,38	2-10
PDI 1	5,42	2-10
PDI 3	5,22	2-10
PDI 6	4,98	2-10
PDI 12	5,06	2-10

Table 1: This table shows descriptive statistic with media and standard deviation of pain intensity, anxiety, depression and pain disability variables evaluated at baseline,1 month follow up,3 month follow up,6 month follow up,12 month follow up; Legenda: VAS BL: Vas measured at baseline; VAS 1:Vas measured at 1 month follow up; VAS 3: Vas measured at 3 month follow up; VAS 6: Vas measured at 6 month follow up ; VAS 12:Vas measured at 12 month follow up; ANX BL: Anxiety measured at baseline; ANX3:Anxiety measured at 3 month follow up; ANX 6: Anxiety measured at 6 month follow up ; ANX 12:Anxiety measured at 12 month follow up; DEP BL: Depression measured at baseline; DEP3:Depression measured at 3 month follow up; DEP 6: Depression measured at 6 month follow up ; DEP 12:Depression measured at 12 month follow up; PDI BL: Pain disability measured at baseline;PDI1:Pain disability measured at 1 month follow up; PDI 3: Pain disability measured at 3 month follow up; PDI 6: Pain disability measured at 6 month follow up; PDI 12:Pain disability measured at 12 month follow up.

Figure 1: This table shows the frequency distribution of chronic illnesses in the sample; Legenda: FB: Fibromyalgia; RD: Radiculopathy; HEAD: Headache; ARTHR: Arthritis; NEURPAIN: Other clinical conditions characterized by neuropathic pain: OTHER: Other clinical conditions characterized by chronic pain.

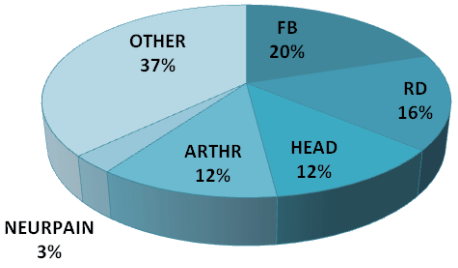

Fig. 1. Chronic Pain Conditions of 338 subjects

During the follow-up 124 patients interrupted the therapy, 79 of them for inefficacy, 33 of them for side effects, especially sleepiness (30%) and mental confusion (25%) maybe because of high percentage of Bedrocan' THC (19%) (Fig 2; Fig 3).

Figure 2: The graphic shows the reasons of interruption after the first month of therapy.

Figure 3: The graphic shows the distribution (frequency) of side effects reported by 33 subjects who suspended therapy at 1month follow up.

These adverse symptoms regressed soon after the cessation of cannabis. No side effect was judge to be due to interaction with other conventional remedies.

Adverse events are more common during cannabinoid treatment compared to the control treatment and are most frequently sedation like symptoms (24) 214 patients completed the follow-up and continued the therapy for (at least) 12 months.

After 12 months of therapy, pain intensity, pain disability, anxiety and depression show a substantial improvement (Tab. 1).

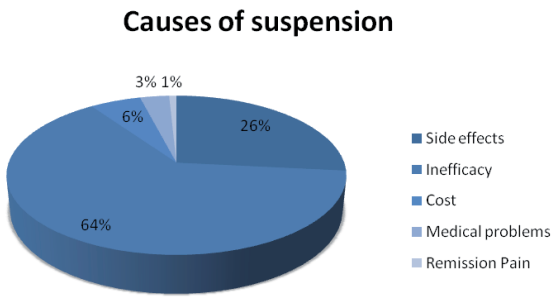

Fig. 2. Causes of 124 patient's suspension

A Friedman test was conducted to evaluate differences in medians among the vas baseline (Median = 9.00), VAS follow up 1 month (Median = 7.00), VAS follow up 3 months (Median = 6.00), VAS follow up 6 months (Median = 5.00), VAS follow up 12 months (Median = 5.00). The test was significant χ 2 = 61.375, p < .001. Follow-up pairwise comparisons show that median concern for VAS baseline was significantly greater than VAS concern follow up 1 month (Z = 1.426, p < .01), follow up 3 months (Z = 1.833, p < 001), follow up 6 months (Z = 2.389, p < 001), follow up 12 months (Z = 2.500, p < .001).

Friedman test was used, also, to compare differences among Median values of variable Pain disability at baseline (Median=6.28) follow up 1 month (Median=6),follow up 3 month (Median 3 month=6),follow up 6 month (Median=5.57) and follow up 12 month (Median=5.93).

The test was significant χ 2 =39.423, p < .001. Follow-up pairwise comparisons show statistical significance only for differences between Pain disability baseline and follow up 3 month (Z =1.519, p < .01), Pain disability baseline and follow up 6 month (Z =1.741, p < .01), Pain disability baseline and follow up 12 month (Z = 1.556, p < .01) (Fig. 4).

Figure 4: This graph shows the Median values of Pain Intensity (VAS) and Pain Disability (PDI) at baseline and 1month follow up,3 month follow up,6 month follow up,12 month follow up.

Pairwise comparison reveals that only differences between VAS BL and follow up are significant but not differences between3 month and 6 month follow up, 3 month and 12 month follow up, 6 month and 12 month follow up.

Pairwise comparison demonstrate that only differences between Pain disabiliy Baseline and 3 month,6 month and 12 month follow up are significant

According this result therapy seems improves its efficacy only during the first three months, then became stationary; it seems to be in agreement to the clinical observations. However, it is important to consider that this is an observational study and that samples are small.

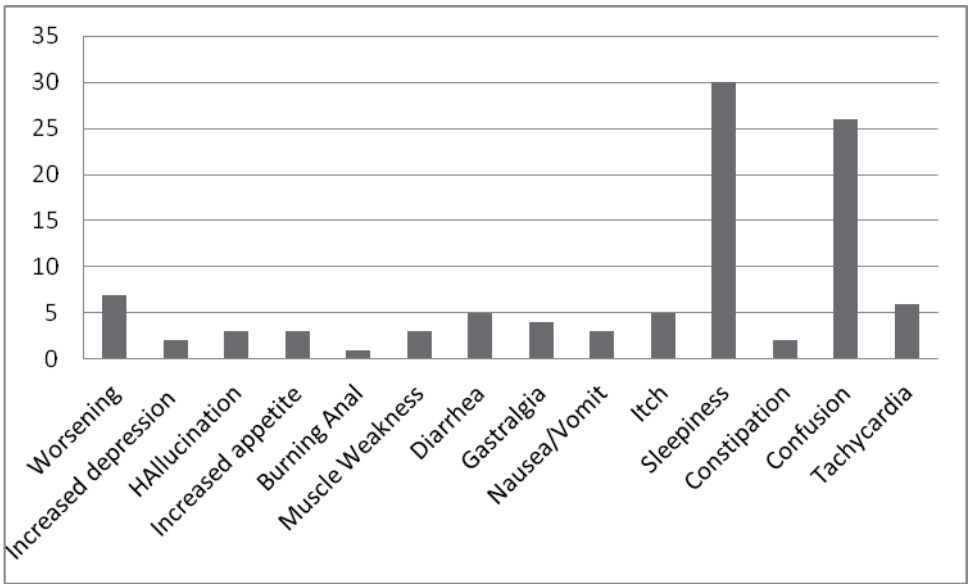

Fig. 3. Side effects that caused suspension of therapy.

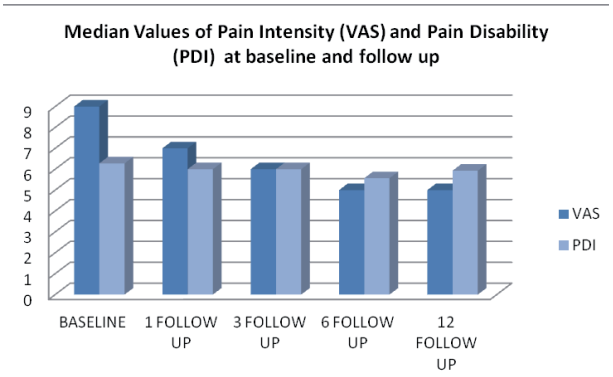

Fig. 4. Median Values of Pain Intensity and Pain Disability at baseline and follow up.

We also observed significant results comparing median values of anxiety at baseline (Median=8), follow up 3 month (Median=5),follow up 6 month (Median=5) and follow up 12 month (Median=5).

The test was significant χ 2 =30.362, ($p < .001$) and the follow-up pairwise comparisons show that differences between anxiety at baseline and follow up 3 month (1.093, $p < .05$),anxiety baseline and follow up 6 month ($Z = 1.222$, $p < .01$), anxiety baseline and follow up 6 month ($Z = 1.093$, $p < .05$) are significant

Similar results were obtained using Wilconson test for median values of depression baseline(Median=11), follow up 3 month (Median 3 month=6),follow up 6 month (Median=5) and follow up 12 month (Median=5):the test was significant χ 2 =27.786, ($p < .001$) and the follow-up pairwise comparisons show that differences between depression at baseline and follow up 3 month (1.000, $p < .05$),depression baseline and follow up 6 month ($Z = 1.241$, $p < .01$), anxiety baseline and follow up 6 month ($Z = 1.019$, $p < .05$) are significant (Fig.5).

Figure 5: This graph shows the Median values of Anxiety and Depression at baseline,3 month follow up,6 month follow up,12 month follow up.

Pairwise comparison demonstrate that only differences between Anxiety and Depression Baseline and 3 month,6 month and 12 month follow up are significant.

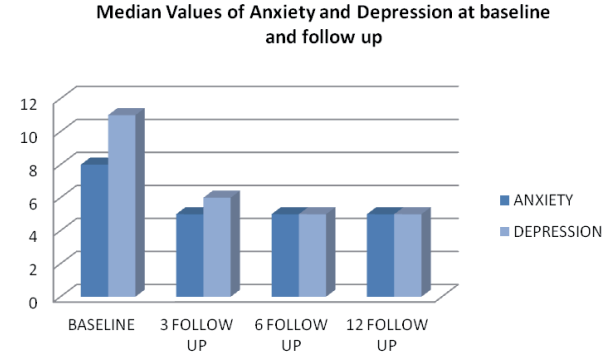

Fig. 5.Median Values of Anxiety and Depression at baseline and follow up

Design of our study not permits to assess that Cannabis therapy is more effective than other treatments because there is no control group and the aim is only observational: however, our results suggest that using of medical Cannabis can be a valid adjunct to traditional pharmacological therapy of chronic pain, in most cases represented by opiates (18)

It not possible to discriminate the effect of Cannabis and of pharmacological therapy on pain relief, although the doses used in our study, ranged from 5 to 40 mg, corresponding to 28 to 210 mg of cannabis, are similar to those proved effective in other studies (25-27) As stated in a systematic review, the current evidence suggests that very low-dose medical marijuana (< 34 mg per day) is associated with an improvement in refractory neuropathic pain of moderate severity in adults using concurrent analgesics (12).

Further study are necessary to measure and compare effects among Cannabis therapy, traditional analgesic therapy and placebo on pain relief.

What our research highlights is the possible conjuction of Cannabis therapy and analgesic drugs in order to obtain not only a greater reduction of pain intensity but also greater improvements on daily functionality and psychological state (18).

Although our results are significant only in relation with baseline, demonstrating that improvements are not stable in the long term, but it is possible that this lack of significance among median values at 3, 6 and 12 months is linked to no homogeneity and size of sample.

Another result of our study is represented by an improvement of pain disability: the surveyed subjects who could not perform their normal daily activities because of pain, improved after cannabis treatment: it is possible that this improvement is a consequence of less pain intensity. Cannabis proved to substantially decrease anxiety and depression, two features that are strictly related to chronic pain. Continuous pain does not allow patients to lead a serene and relaxed life during the day. We observed that symptoms of depression and anxiety decreased, as reported in literature where cannabinoids showed therapeutical potential in psychiatric disorders (28-29).

Discussion

Chronic pain is not easy condition to treat and represent a widespread problem especially in hospital setting (30)

Our research demonstrate that Cannabis therapy, as an adjunt to traditional analgesic treatment, reduces pain intensity, improves daily functionality and it allows a reduction in anxiety and depression symptoms. However, Cannabis is not the answer to everyone's pain.

Cannabis should be prescribed responsibly by taking into account the comprehensive pain history of the patients, obtaining informed consent after discussing the risks and benefits of treatment and administering periodic follow-up of the treatment efficacy.

Our study is only a trial, so randomized controlled trials and further analysis are needed to demonstrate if cannabis therapy is more effective than traditional analgesic therapy and for what reasons.

The lack of double blind method may have given bias both in the patients and in the researchers who have collected data. Moreover, there was a significant drop-out rate, another possible source of selection bias: a large proportion of patients were lost to the particularities of the therapy. Cannabis is still not considered a drug like the others and this causes problems that in the case of other treatments are not found. For example, in our statistics 38 patients did not take cannabis because of their negative prejudices regarding it, simply seen as a drug of abuse and not as a medicament. Even, 87 patients have been unable to obtain the medication as absent in pharmacies. As mentioned, medical cannabis is imported from the Netherlands and distributed to galenic pharmacy who request it but, due to bureaucratic difficulties, very few Italian pharmacies are still able to procure it. Conversely, many people place in cannabis miraculous expectations, supported by bad information, in particular on the internet. These expectations collide with the reality of the difficulties that there are to treat chronic conditions and so 10 patients discontinued therapy after only a week because they did not see immediate results. Some of these aspects (difficulties to gain access of cannabis, regulatory barriers) are common in cannabis and cannabinoid research, as shown in literature (12).

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