Research Work

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Medical Cannabis in Patients with Chronic Pain: Effect on Pain-Relief, Pain Disability, and Psychological aspects . An Observational Study

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There is an increasing interest in the medical use of cannabis, particularly in the treatment of chronic pain.
The aim is to evaluate the effects of cannabis use and the associated benefits reported by patients with various chronic pain diagnoses.
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.
Cannabis use in patients with chronic pain shows an improvement of pain, pain disability, anxiety and depression symptoms.
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.

1.1 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 (6) According to the increased knowledge of the endocannabinoid system, the preclinical work and the results from different animal models, cannabinoid agonists could be analgesic (7-13). These findings highlight the potential role of cannabis in pain management and preliminary evidence from clinical studies supports this data (14-21) 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 (22-25).
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” (26). Pain syndromes with a positive response to cannabinergic therapies include chronic neuropathic pain some kind cancer pain, spasticity, acute pain and chronic pain conditions (27-31). 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 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 (32).

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

1.2. 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 observational 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 (33). 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

Psychopatology;

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

Psychopathology: The M.I.N.I. International Neuropsychiatric Interview (34) 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 conceivable 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 (35) 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 (36-37) 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

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%.

1.3 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 (Tab1;Fig 1)
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 (43) 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 (Tab1)
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)
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.
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).
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 (32)
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 (39-41) 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 (21)

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 (32)
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 (42- 43).

1.4 DISCUSSION

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 observational, 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 (26)

1.5 GRAPHS AND TABLES

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

Variables		
Age	60 (Xm)	14 (Ds)
Sex (M)	34%	
Sex (F)	66%	
	Xm	**Ds**
VAS BL	8,63	2,11
VAS 1	6,56	2,35
VAS 3	6,11	2,42
VAS 6	5,33	2,57
VAS 12	5,37	2,57
ANX BL	8,85	4,9
ANX 3	5,52	3,86
ANX 6	5,56	4,25
ANX 12	5,81	3,98
DEP BL	10,3	5
DEP 3	7,04	4,93
DEP 6	6,19	4,73
DEP 12	6,7	4,45
PDI BL	6,38	2,04
PDI 1	5,42	2,12
PDI 3	5,22	2,27
PDI 6	4,98	2,46
PDI 12	5,06	2,51

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; Xm: Media; Ds: standard deviation

Figure 1: Chronic Pain Conditions of 338 subjects

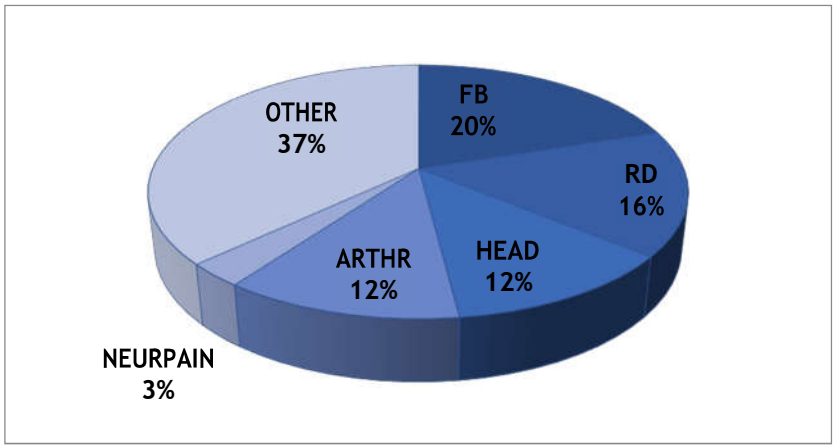

Figure 1: This table shows the frequency distribution of chronic illnesses in the sample; Legenda: FB: Fibromyalgia; RD: Radiculopathy; HEAD: Headache; ARTHR: Arthritis; NEURPAIN: Other clinical conditions characterized by neuropathic pain: OTHER: Other clinical conditions characterized by chronic pain

Figure 2: Causes of 124 patient's suspension

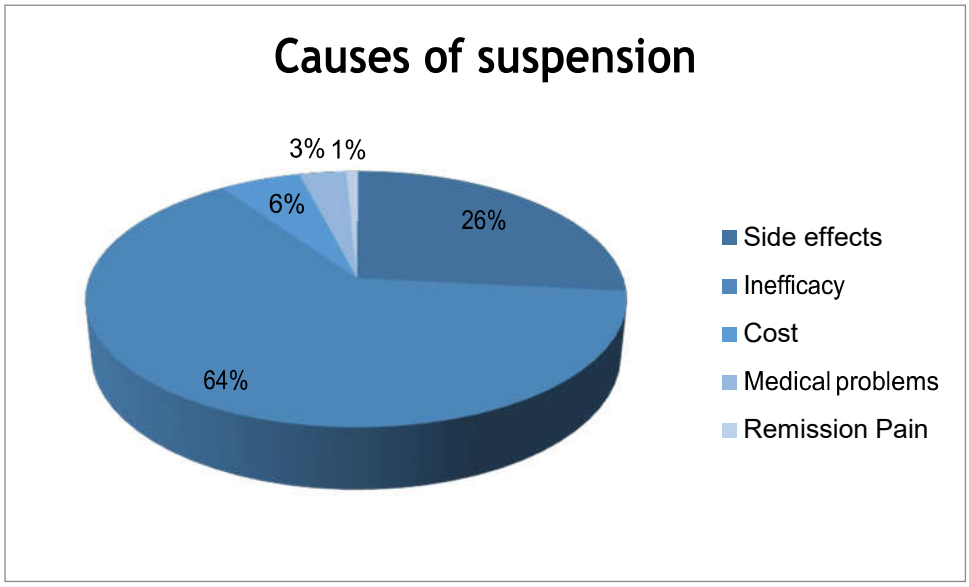

Figure 2: The graphic shows the reasons of interruption after the first month of therapy

Figure 3: Side effects that caused suspension of therapy

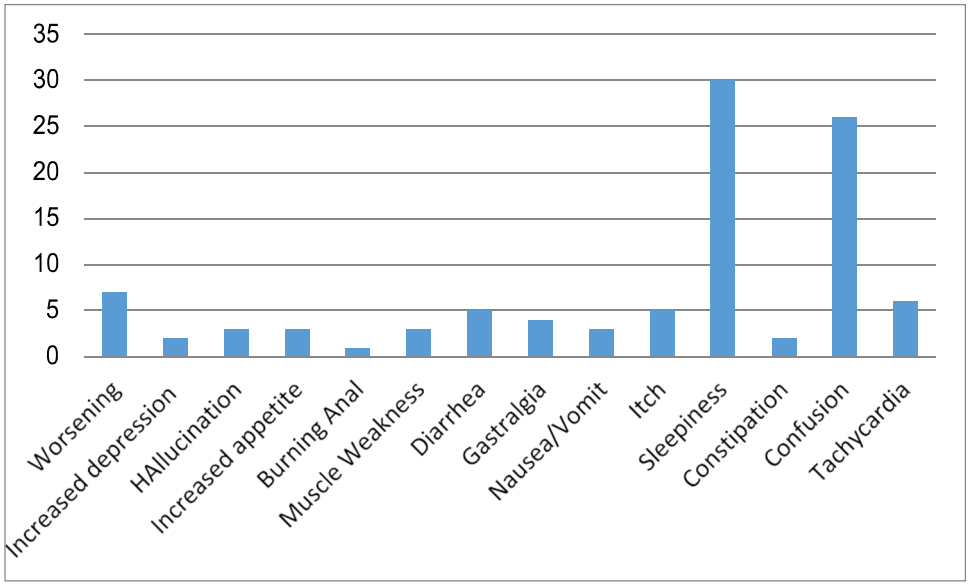

Figure 3: The graphic shows the distribution (frequency) of side effects reported by 33 subjects who suspended therapy at 1month follow up

Figure 4: Median Values of Pain Intensity and Pain Disability at baseline and follow up

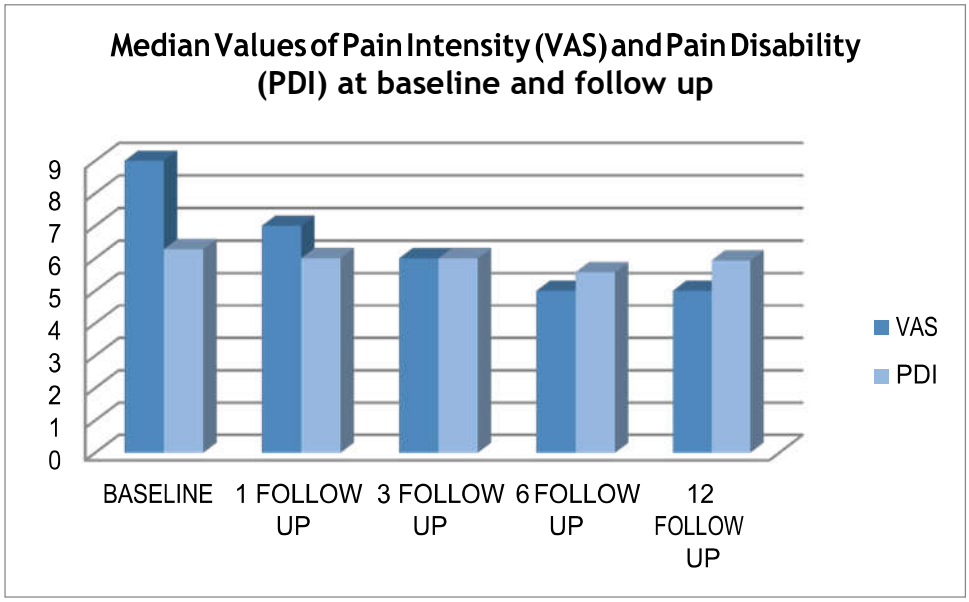

Figure 4: This graph shows the Median values of Pain Intensity (VAS) and Pain Disability (PDI) at baseline and 1month follow up,3 month follow up,6 month follow up,12 month follow up.
Pairwise comparison reveals that only differences between VAS BL and follow up are significant but not differences between3 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

Figure 5:Median Values of Anxiety and Depression at baseline and follow up

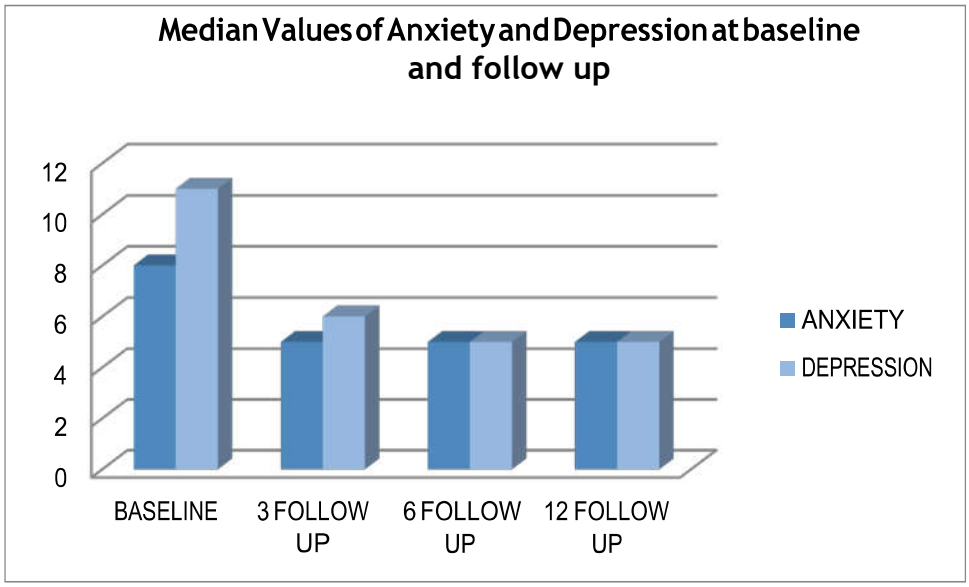

Figure 5: This graph shows the Median values of Anxiety and Depression at baseline,3 month follow up,6 month follow up,12 month follow up.
Pairwise comparison demonstrate that only differences between Anxiety and Depression Baseline and 3 month,6 month and 12 month follow up are significant.

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Comparison between Cannabis Flos and Cannabis FM2 effects on Chronic Neuropatic Pain

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Cannabis based drugs are often prescribed in order to obtain pain relief and muscle relaxation: for this purpose are prescribed Cannabis based drugs with balanced ratio between Cannabis Flos (THC 6% and CBD 8%) or Italian Cannabis FM2 (THC 5-8% and CBD 7-12).
The aim of this study is to assess if there are significative differences betweenCannabis Flos (THC 6% and CBD 8%) and Cannabis FM2 (THC 5-8% and CBD 7-12) effects on chronic neuropathic pain. Variables compared were pain intensity (VAS), frequence of side effects, frequence in the use of traditional analgesic drugs; Psychopatological dimensions were evaluated with Hospital Anxiety and Depression Scale (HADS). Our study suggest a better effect of Cannabis FM2 treatment, not on pain intensity but only on qualitative aspects associated to pain experience, as use of traditional analgesic drugs, frequence of side effects and psychological conditions. Further studies are needed to confirm our conclusions.

2.1 INTRODUCTION

The long journey of Medical Cannabis in Italy begins in 1998 when the Italian State approves and regulates the prescription of Cannabis based preparations for therapeutic use (DI Bella law)(1): these preparations were not considered drugs and their composition varied according to the needs of patients, so there was no standardization.
Only in 2007 delta-9-tetrahydrocannabinol and dronabinol are included in a official list of drugs (Tabella dei Medicinali, section B) by Ministry of Health and in 2013 are also included Cannabis based vegetable substances (2).
Thanks to these laws since 2007 it has been possible to import from Holland, in particolar from Bedrocan Industry, drugs as Bedrocan or Bediol.
This drugs, based on Cannabis sativa,can be administered orally (e.g through infusions in olive oil) ora via inhalation and have different THC and CBD concentrations: Bedrocan's constituents are 22% THC and < 1% CBD, while Bediol contains 6,5% THC and 8% CBD.
The use of these drugs has been documented in many clinical conditions, expecially in treating chronic pain. According to recent review pain management is the the main reason for requesting and using Cannabis, a needed by 45-80% of patients using Cannabis based drugs alone or for 39% of patients using it as an adjunct to traditional opioid therapy (3-7).
the Italian law of 2015 has authorized the use of Cannabis to improve analgesic effects not only for neuropathic pain but also for all chronic pain conditions "when other available medications have proven to be ineffective or inadeguate to the therapeutic need for patients" (8).
An important change in the use of Medical Cannabis in Italy it was, due to agreement between Ministry of Health and Ministry of Defense,the beginning of italian production of Cannabis and its availaibility, since February of 2017,of FM2 (9-10).
FM2 is a Cannabis based drug product by Military Chemical Pharmaceutical Factory, in Florence, according to the Good Manufacturing Practices (GMP)(11)
It is constituted by feminine inflorescences not fertilized of Cannabis plant,dried and planted in ground with 5-8% of THC and 7,5-12% of CBD.
The birth of FM2 represent an important change not only for the patients but also for the italian economy: the production within the country should ensure a greater availability and lower cost, although, during last months, there have been issues which have not provided a sufficient supplying.
Moreover, FM2 allows to reduce importation costs and it is the first attempt, in Europe, to adopt an industrial approach in this field even though under the control and supervision of Italian Agency of Drug (AIFA).

Cannabis in Chronic Neuropatic Pain: Bediol and FM2

Recently several meta-analysis and systematic reviews tried to make the point on the efficacy of Cannabis in chronic pain, showing that there was at least moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain (12-15); Pain syndromes with a positive response to cannabinergic therapies include chronic neuropathic pain for some kind cancer pain, spasticity, acute pain and chronic pain conditions (16-20). A recent review of National Academies of Sciences, Engineering and Medicine assess the evidence for the effectiveness of Cannabis in chronic pain, but the strength of these results are low and limited to neuropathic pain (21).
Moreover data often comes from research and studies which employs different concentrations of THC and CBD making difficult to compare results obtained (22).
Bediol and FM2 ,unlike Bedrocan, which contains mostly THC, shows a more balanced ratio between the two main components.
It has been suggested that the presence of Cannabidiol (CBD) ameliorates the psycho-active effects of delta-9-tetrahydrocannabinol (THC): CBD blocks the methabolism of THC to 11-hydroxt-THC, more psicho-active than THC and may produces dysphoria (23-24).
So if it is comprehensible that Bedrocan and Bediol have different effects, because of THC predominante on one side, and more balance ratio THC:CBD on the other,there are no still data concerning the comparison between Bediol and FM2 effects on chronic neuropathic pain.
The aim of this study is to assess if there are significative differences on pain relief, on side effects , on use of traditional analgesic drugs and on psychological aspects between two different groups of subjects with chronic neuropathic pain, one treated with Bediol and the other one with FM2.

2.2 MATERIALS AND METHODS

At the Poli Pain Clinic we recruited, after their informed consent, 108 subjects affected by various form of chronic pain: according to pain therapist they have received a different Cannabis based drug prescription, in particular Bediol® and FM2®.
The Bediol Group (N 58) and FM2 Group (N 59) were evaluated at baseline, 3 months and 6 months follow up: the variables investigated at every evaluation are divided into clinical and psychological variables.
Clinical variables are Pain intensity (VAS), side Effects, use of traditional analgesic drug; Psychological Variables are anxiety and depression symptoms measured with Hospital Anxiety and Depression Scale (HADS) (26).
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.

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

Cannabis was administered orally, through infusions in olive oil: the prescription for the pharmacy, responsible of preparation, was 1 gram of Medical Cannabis every 10 gram of olive oil.

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 assumption, suggesting sublingual intake in order to speed up metabolism of Cannabis compounds.

During six months of evaluation, most patients continued to take their traditional analgesic therapy in addition to Cannabis therapy.

To evaluate the survey variables we used different tools in order to obtain a quantitative measurement of clinical and psychological dimension:

- 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 conceivable pain” (10 value).

- Depression and anxiety symptoms: The Hospital Anxiety and Depression Scale (HADS) is a self-assessment scale developed to detect states of depression, anxiety and emotional distress among patients affected by organic pathologies, discriminating between psychopatological and somatic symptoms. It is composed by ~~a~~ fourteen items: seven of them relate to anxiety and seven ~~r~~relate to depression (25-26)

All measurement (VAS, HADS), performed at the Baseline, were repeated, with telephone interviews, 3 months and 6 months after the onset of therapy and were used as outcome measures.

Statistical methods

Data were analysed using the SPSS software (version 23.0.1)
Trends of Pain Intensity in each group was evaluated with paired Sample T test
Comparison between Bediol and FM2 groups about Pain intensity and HADS scores at Baseline, 3 and 6 months follow up were conducted with Independent Sample T Test.

Chi-square test was used to assess the presence of relationship between Cannabis treatment and frequence of analgesic use; Chi-Square test was used also to evaluate link between Cannabis treatment and side effects frequence.
Statistical significance was at 5%

2.3 RESULTS

Our sample was composed by 116 subjects divided into Bediol group (n.57) and FM2 group (n.59) according their clinical prescriptions (Table 1)
Bediol group was composed by 43 women and 14 men, mean age 49 ± 13, affected by fibromyalgia (54%), arthritis (8%), headache (7%)and various forms of neuropathic pain (28%).
FM2 group was composed by 51 women and 8 men, mean age 53 ± 15, affected by fibromyalgia (64%), arthritis (5%), headache (10%) and various form of neuropathic pain (19%) (Figure1A;1B)
There were no statistically significant differences between Bediol group and FM2 group in any demographic (age and sex) and clinical variables (diseases distribution).
After completing data collection, we have verify the presence or not of statistically differences between two groups regarding Pain intensity at Baseline, 3 month follow up, 6 month follow up. (Figure 2)
In order to have a measurement of Bediol/FM2 effects on VAS scores we have calculated three kind of ΔVAS, for both groups, obtained by the difference between VAS Baseline and VAS three months follow up (ΔVAS BL), difference between VAS three months follow up and VAS six months follow up (ΔVAS 3), difference between VAS Baseline and VAS six months follow up (ΔVAS 6).
Test T for independent sample revealed no statistically differences between ΔVAS BL of Bediol and FM2 ($t(116) = -1,1$; $p>0,05$), between ΔVAS 3 ($t(116) = 0,99$; $p>0,05$) and between ΔVAS 6 ($t(116) = 0,6$ $p>0,05$).
Data suggests that effects of Bediol and FM2 on pain intensity are not different over time.(Table 2)
Another important data that indirectly could suggest the lack of differences between two groups is represented by the presence of same mechanisms: indeed, in each group, paired sample T test highlights that the reduction of pain intensity at 3 months follow up and 6 months follow up is statistically significant only for differences between Baseline and 3 months follow up and Baseline and 6 months follow up (FM2 group differences between Baseline and 3 months follow up $t(58) = 5,17$; $p<0,05$; differences between Baseline and 6 month follow up $t(58) = 4,34$; $p< 0,05$; Bediol group differences between Baseline and 3 months follow up $t(56) = 3,59$; $p<0,05$; differences between Baseline and 6 month follow up $t(56) = 3,24$; $p< 0,05$)
This similar trend could indicate that both Bediol and FM2, as Cannabis based drugs, leads to a significant reduction of pain intensity which then stabilize itself over time.
The association between kind of Cannabis treatment and frequence of sides effects was evaluated with X square test: for each step (Baseline, 3 month follow up, 6 month follow

up) was examined the presence of statistically relationship between time, independent variable, and frequence of side effects, considered dependent variable.
These analyzes was conducted both in Bediol group and FM2 group.
Results demonstrated only a statistically significant relationship at 6 month follow up (X^2 = 5,78; p< 0,05) so, in FM2 group registered adverse effects are less frequent than in Bediol group (Table 3; Figure 3)
Another important examined association was the link between kind of treatment and frequency of analgesic use: the analysis process is the same to that reported above.
Also in this case, results demonstrated only a statistically significant relationship at 6 months follow up (X^2 6,24; p<0,05)showing a less using of analgesics drugs in FM2 group than in Bediol group.(Table 4; Figure 4)
Regarding Psychological dimensions, variables examined were ΔHADS and in particular: ΔHADS ANX, for both groups, obtained by the difference between HADS Anxiety scores at Baseline and HADS Anxiety scores at three months follow up (ΔHADS ANX BL), difference between HADS Anxiety scores three months follow up and HADS Anxiety scores six months follow up (ΔHADS ANX 3), difference between HADS Anxiety scores Baseline and HADS Anxiety scores six months follow up (ΔHADS ANX6).
ΔHADS DEP (ΔHADS DEP BL, ΔHADS DEP 3 ΔHADS DEP 6) and ΔHADS TOT (ΔHADS DEP BL, ΔHADS DEP 3 ΔHADS DEP 6) were calculated with the same process reported above.
Data analysis demonstrated that a ΔHADS ANX 6 and ΔHADS DEP 6 in FM2 group were greater in a statistically significant way, than in Bediol group (t 2,27; p< 0,05; t 3,53: p<0,05), so in FM2 group was registered a greater reduction of anxiety and depression symptoms compared to Baseline than in Bediol group, at 6 month follow up (Table 5)

2.4 DISCUSSION

Literature about Medical Cannabis use in neuropathic pain confirm the presence of effectiveness evidence, although with low strength, by Cannabis preparations with standardized ratio THC-CBD (21).
This result also emerged from our study: indeed, during six months of evaluation, in both groups there is a reduction of pain intensity although it is significant only in the first three months.
Further analyses are necessary in order to investigate better the significance in pain reduction limited to three months: effects of size and lack of homogeneity of sample or demonstration of stabilizing effects? Recent review asses the difficult to give an answer to this question due to small studies and limited follow up over time (27).
Regarding the comparison between Bediol and FM2 is it important to underline that the aim of this study is not to assess the effectiveness of a Cannabis based drug compared to another one, but verify only the presence of differences between Bediol and FM2, in a observational perspective.

In FM2 group we observed a better effect on chronic neuropathic pain represented by a less frequence of traditional analgesic drug use, although results not demonstrate a greater significant reduction in pain intensity, compared to Bediol group.
However, in Bediol group the frequence use of analgesic drugs , the frequence of side effects was significant greater than data registered in FM2 group.
So it is possible speculate that if from a quantitative point of view there are no differences on chronic neuropathic pain, differences are present from a qualitative point of view: although the same variance in pain reduction, subjects in FM2 group tolerate less side effects and they need less to make use of traditional analgesic drug.
Regarding psychological variables it possible to applying the same reasoning: one the one hand no significant differences in pain intensity reduction, on the other a significant greater reduction of anxiety and depression symptoms in FM2 group compared to Bediol group.
Based on this data also psychological aspects could represent a qualitative dimension linked to pain experience that registered a greater improvement in FM2 group.
Our study suggest better qualitative conditions associated to pain reduction in FM2 treatment compared to Bediol treatment after six months of evaluation.
Further studies are needed to confirm our conclusions and to carry out more detailed investigations regarding relations between variables analyzed and regarding reasons for which we have recorded these observations.

2.5 GRAPHS AND TABLES

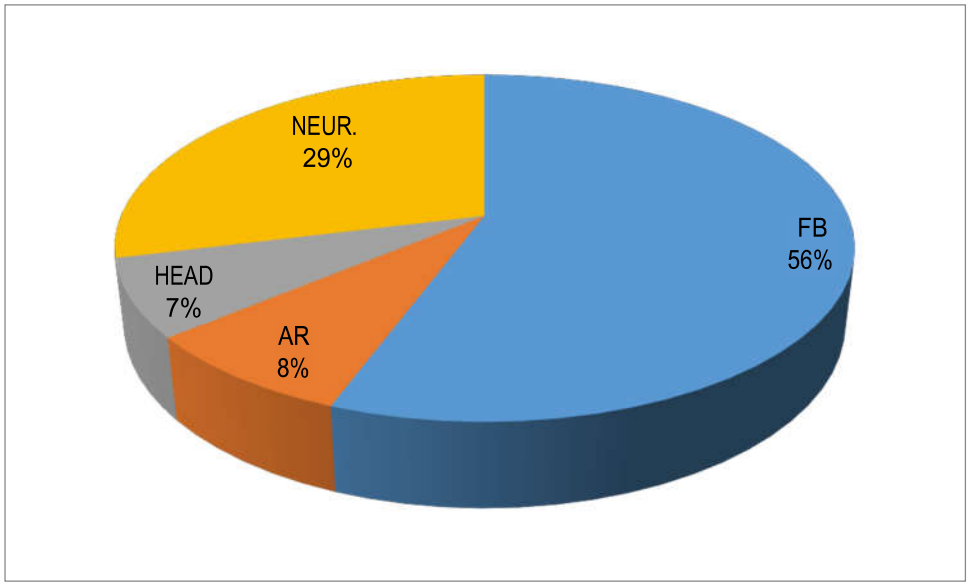
Table 1: Descriptive statistic and Clinic Variables at Baseline and Follow up

VARIABLES	BEDIOL GROUP(n.57)		FM2 GROUP (n.59)	
	75,4% (F) 24,6% (M)		86,4% (F)	15,6% (M)
	XM	**DS**	**XM**	**DS**
AGE	49,31	13,80	53,54	15,11
VASBL	6,31	2,25	7,59	1,83
VAS3	5,00	2,41	5,68	2,74
VAS6	4,32	3,11	5,26	2,61
HADS ANX BL	10,31	5,53	16,69	6,62
HADS DEP BL	7,00	3,74	8,44	3,98
HADS TOT BL	9,64	3,81	15,78	7,68
HADS ANX 3	6,55	4,29	6,64	3,98
HADS DEP 3	9,12	3,98	8,72	5,48
HADS TOT 3	13,00	6,91	13,86	5,83
HADS ANX 6	5,78	5,16	6,52	3,44
HADS DEP 6	8,07	4,04	7,91	2,79
HADS TOT 6	13,00	6,91	14,22	5,02

Table 1: This table shows descriptive statistic with media and standard deviation of pain intensity, anxiety and depression variables evaluated at baseline, ,3 month follow up,6 month follow up, for each group.

Legenda: VAS BL: Vas measured at baseline; VAS 3: Vas measured at 3 month follow up; VAS 6: Vas measured at 6 month follow up ;HADS ANX BL: Anxiety measured at baseline; HADS ANX3:Anxiety measured at 3 month follow up; HADS ANX 6: Anxiety measured at 6 month follow up ; HADS DEP BL: Depression measured at baseline; HADS DEP3:Depression measured at 3 month follow up; HADS DEP 6: Depression measured at 6 month follow up ; HADS TOT BL: Total Anxiety and Depression symptoms measured at baseline; HADS TOT 3: Total Anxiety and Depression symptoms measured at 3 month follow up;

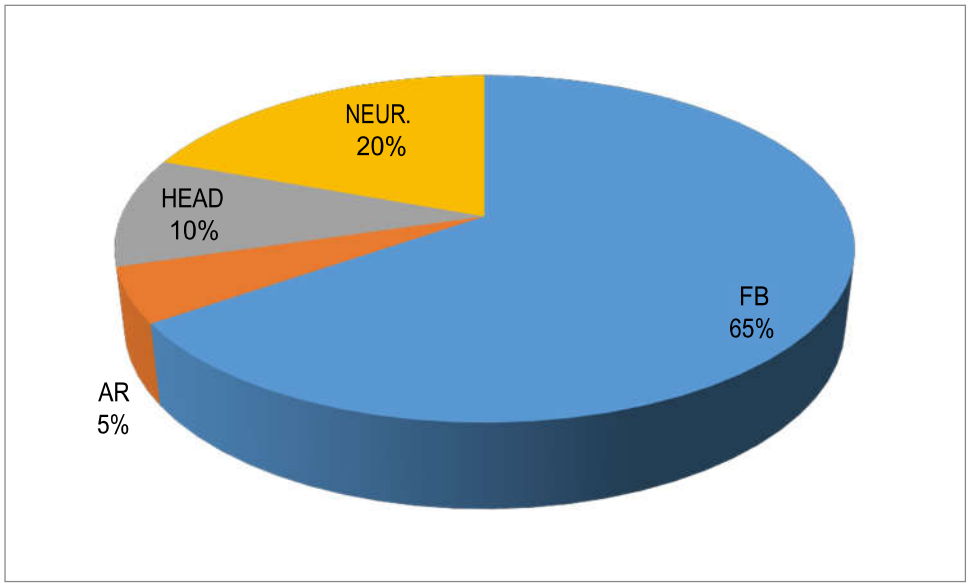
Figure 1A: Neuropatic Chronic Pain Conditions of Bediol Group



This table shows the frequency distribution of chronic illnesses in the Bediol sample

Legenda: FB: Fibromyalgia; HEAD: Headache; AR: Arthritis; NEUR: Other clinical conditions characterized by neuropathic pain

Figure 1B: Neuropatic Chronic Pain Conditions of FM2 Group



This table shows the frequency distribution of chronic illnesses in the FM2 sample

Legenda: FB: Fibromyalgia; HEAD: Headache; AR: Arthritis; NEUR: Other clinical conditions characterized by neuropathic pain

Figure 2: Trends of Pain Intensity (XM) in Bediol and FM2 Group

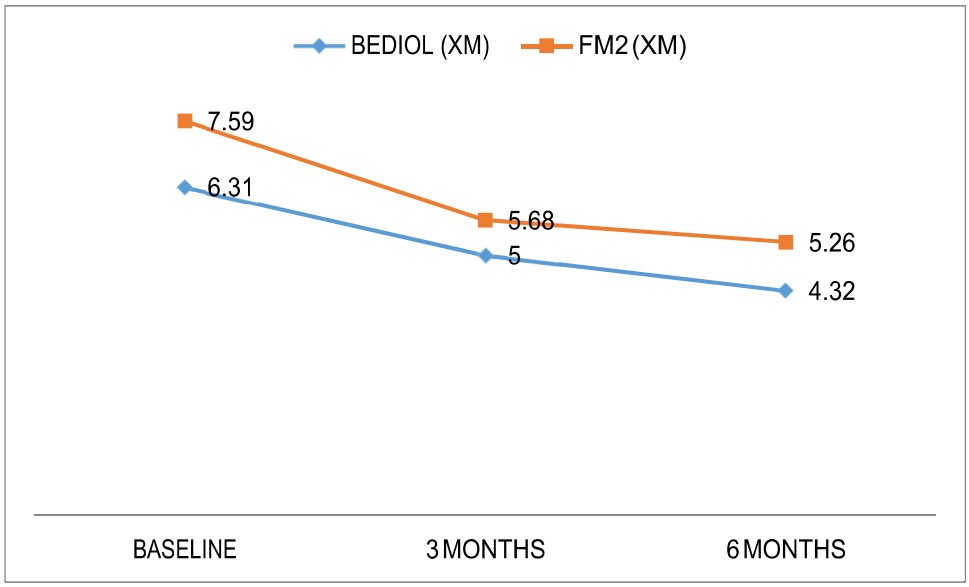


Table 2: Descriptive and Inferential Statistic about Differences in Pain Intensity (ΔVAS)

TIME		BEDIOL			FM2			P
		Xm	Ds	t(GL)	Xm	Ds	t(GL)	
Δ VAS BL	1,33	2,79	3,59(56)		1,92	2,81	5,17(58)	p<0,05
Δ VAS3	0,02	2,05			0,52	2,10		
Δ VAS 6	1,70	3,07	3,24(56)		2,14	2,88	3,34(58)	p<0,05

The table shows media and standard deviation of differences in VAS scores (ΔVAS) at Baseline, follow up 3 months, follow up 6 months in Bediol and FM2 group.
The table contains also data obtained by Student T test and corresponding P value.

Legenda: Δ VAS BL: differences beetween VAS scores at Baseline and VAS scores at 3 months follow up; Δ VAS 3: differences beetween VAS scores at 3 months follow up and VAS scores at 6 months follow up; Δ VAS 6: differences beetween VAS scores at Baseline and VAS scores at 6 months follow up; Xm: media; Ds:Standard deviation ; t(GL): T score and degrees of freedom; P: p value

Table 3: Frequence of Side effects reported in Bediol and FM2 Group at 3 months and 6 months follow up

SIDE EFFECTS	BEDIOL FOLLOW UP 3	FM2 FOLLOW UP 3	BEDIOL FOLLOW UP 6	FM2 FOLLOW UP 6
NO SIDE EFFECTS	64,4	78	72,2	89,8
CONFUSION	16,9	8,5	11,1	3,4
TACHYCARDIA	3,4	0	5,6	0
DRYMOUTH	3,4	1,7	3,7	1,7
SLEEPINESS	5,1	6,8	1,9	3,4
MULTIPLE SIDE EFFECTS	4,8	1,7	3,7	1,7
RESTLESSNESS	0	3,4	1,9	0

The table shows,frequence of side effects registered at 3 month follow up and 6 month follow up in each group

Figure 3: Graphic representation of side effects distribution in Bediol and FM2 group at 3 months and 6 months follow up

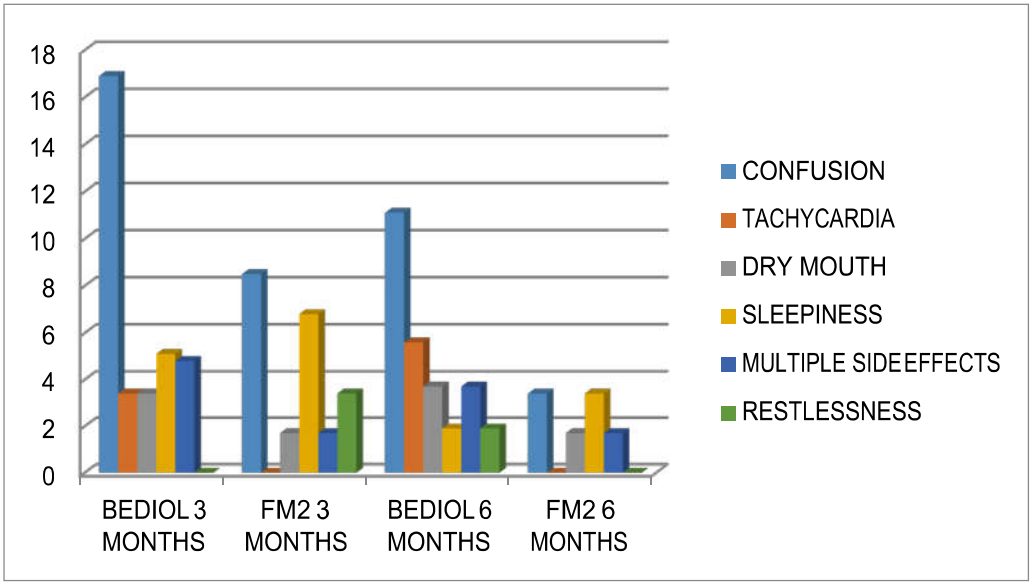


Table 4: Percentage of Traditional analgesic use

	THERAPYDOL IN BEDIOL	THERAPYDOL IN FM2
BASELINE	54,40%	57,60%
FOLLOW UP 3 MONTHS	50,90%	53,70%
FOLLOW UP 6 MONTHS	53,70%	45%

The table shows the percentage of Traditional Analgesic using at Baseline, 3 and 6 months follow up

Legenda: Therapydol in Bediol: Rate of analgesic therapy Use in Bediol group ; Therapydol in FM2: Rate of analgesic therapy Use in FM2 group.

Figure 4: Graphic representation of analgesic therapy Use at Baseline, 3 and 6 months follow up

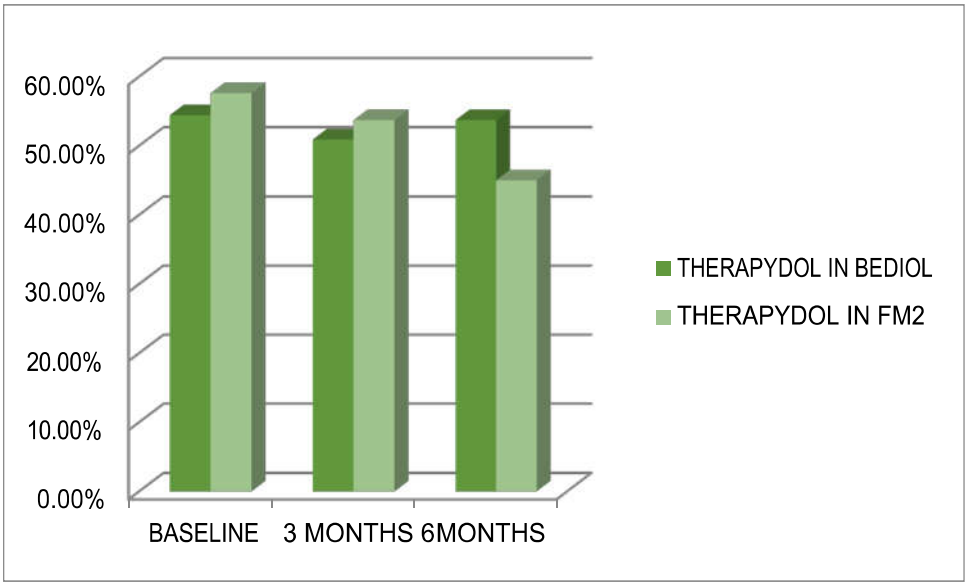


Table 5: Mean Differences among HADS scores (Δ HADS)

TIME	BEDIOL (XM)	FM2 (XM)	P VALUE
Δ HADS BL ANX	2,91	10,31	P<0,05
Δ HADS 3 ANX	-0,19	-0,17	
Δ HADS 6 ANX	4,57	9,89	P<0,05
Δ HADS BL DEP	0,35	0,42	
Δ HADS 3 DEP	-0,11	-0,31	
Δ HADS 6 DEP	-2,1	0,94	P<0,05
Δ HADS BL TOT	-3,4	0,4	
Δ HADS 3 TOT	0,1	0,14	
Δ HADS 6 TOT	-3,28	0,42	

The table shows mean differences among HADS scores measured at Baseline, 3 months and 6 months follow up in Bediol and FM2 group.

Legenda: Δ HADS ANX BL: Difference between HADS anxiety scores measured at Baseline and HADS anxiety scores measured at 3 months follow up; Δ HADS DEP BL: Difference between HADS depression scores measured at Baseline and HADS depression scores measured at 3 months follow up; Δ HADS TOT BL Difference between anxiety and depression total scores measured at Baseline and HADS anxiety and depression total scores measured at 3 months follow up; Δ HADS ANX 3: Difference between HADS anxiety scores measured at 3 months follow up and HADS anxiety scores measured at 6 months follow up; Δ HADS DEP 3: Difference between HADS depression scores measured at 3 months follow up and HADS depression scores measured at 6 months follow up; Δ HADS TOT 3: Difference between anxiety and depression total scores measured at 3 months follow up anxiety and depression total scores measured at 6 months follow up; Δ HADS ANX 6: Difference between HADS anxiety scores measured at Baseline and HADS anxiety scores measured at 6 months follow up; Δ HADS DEP 6: Difference between HADS depression scores measured at Baseline and HADS depression scores measured at 6 months follow up; Δ HADS TOT 6 Difference between anxiety and depression total scores measured at Baseline and HADS anxiety and depression total scores measured at 6 months follow up

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Neurostimulation Therapy integrated with Medical Cannabis: a new way for the management of chronic neuropathic pain?

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Accepted at 9th World Congress of the World Institute of Pain (WIP)

The aim of this observational study is to asses if the intagrated use of Medical Cannabis and Neurostimulation therapy can be leads to a greater improvements on chronic neuropathic pain than Neurostimulation therapy alone.
A group of subjects with chronic neuropathic pain treated with Neurostimulation therapy (N. 35; age 55±13) was compared with a group of subjects (n.40; age 66± 13) affected by various kind of chronic neuropathic pain treated with Neurostimulation therapy integrated with Medical Cannabis assumption.
Our investigations have concerned Pain intensity, measured with Visual Analogue Scale, and psychological dimension measured with Hospital Anxiety and Depression Scale (HADS) at Baseline and at 3 months follow up.
Statistical analyzes revealed that in Medical Cannabis and Neurostimulation group Pain Intensity Difference (ΔVAS) in the period between Baseline and 3 months follow up is greater and statistically significant than the Pain Intensity Difference measured in Neurostimulation group ($t(74)= 2,21$; $p< 0,05$).
Pearson correlations highlights a significant statistically link between variable Age and variable Pain intensity Difference only in Neurostimulation group ($r= -0,81$;n.75 $p= 0,002$)
HADS-D and HADS TOT registered a greater significant reduction in the Medical Cannabis and Neurostimulation group than in Neurostimulation group ($t(74)= 2,71$ $p< 0,05$; $t(74)=3,95$ $p<0,05$)
Our results suggests a better response on chronic neuropahic pain from integrated therapy, Neurostimulation and Medical Cannabis, than from Neurostimulation therapy alone.

Cannabis and Genetic : Genetic influences on Cannabis response in Chronic Pain. Preliminary data

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Definitive Clinical and Genetic data will be presented and discussed for the first time at 1th International Conference of Medical Grade Cannabis

Medical Cannabis is increasingly used in the treatment of chronic pain.
However, in clinical practice there is often a high variability in the treatment response with Medical Cannabis which is not always completely justified by pain intensity or clinical conditions.
The main aim of this research is to describe the presence of a significant association between genetic polymorphisms encoding for cannabinoid receptors and response to treatment with Medical cannabis in chronic neuropathic pain.
In this section only clinical data will be reported, genetic data will be discussed during the presentation.
A group of subjects affected by chronic pain (N.250; Fibromyalgia, Chronic pain, rheumatological diseases, diseases of the Central Nervous System) was evaluated at Baseline, one month follow up and three months follow up.
Variables compared were pain intensity (VAS), frequence of side effects, frequence in use of traditional analgesic drugs; Psychopatological dimensions were evaluated with Hospital Anxiety and Depression Scale (HADS) at Baseline and six months follow up.
Statistical analyzes show that subjects recorded significant reduction in pain intensity at one months (t -2,07 p< 0,05) and three months follow up (t-2,24 p< 0,05) compared to Baseline.
Results demonstrate that significant pain intensity reduction si not correlated with an increase on Medical Cannabis dosage.

Multifactor ANOVA shows that CBD is the variable that most affect the analgesic effect ($p<0,05$) in general sample.
Multifactor ANOVA reveals no significant factors that influence frequence of side effects.
Comparison between subjects taking opioid analgesic therapy and subjects not taking opioid analgesic therapy in addition to Medical Cannabis reveals that in no opioid therapy group reduction of pain intensity is significant greater than in opioid therapy group.
Regarding psychological dimensions anxiety symptoms show a significant reduction ($t-5,56$; $p< 0,05$) compared to baseline.
These results will be crossed with genetic data and will highlight the presence or absence of a significant link between observed clinical variables and genetic factors

4.1 INTRODUCTION

Medical Cannabis is increasingly used in the treatment of chronic pain.
However in clinical practice there is often a high variability in the treatment response with Medical Cannabis that is not always completely justified by pain intensity or clinical conditions.
Moreover, the mechanisms upon which the effect of Medical Cannabis is based have not yet been fully explained.
The aim of our research is to provide a possible link between genetic factor and clinical response to treatment with Medical Cannabis in chronic pain, in order to contribute in an innovative way to greater understanding of the processes through which the cannabinoid system and analgesic functions interact
Recent review has shown that various kind of genes and their polimorphic versions as responsible factors of benefits and adverse effects link to Cannabis therapy.
Our hypothesis is that the presence of particular genetic polymorphisms encoding for cannabinoid receptors register a significant correlation with a different response to Cannabis therapy, not only on pain intensity, but also on dosages, presence of side effects, benefits and indirectly psichological dimension.
in order to test our hypothesis we have collected about 250 samples of genetic material (represented by samples of saliva) provided, after informed consent, by patients affected by various kind of chronic pain (Fibromyalgia,Epilepsy, Diseases of Central Nervous System, Rheumatological Diseases)
Thanks to this data collection we had the possibility to register the trend of response to Cannabis therapy in the medium term.
At the moment we are extracting DNA from the genetic samples and we will be soon able to cross genetic data with clinical data.
The management of chronic pain has always been an area in ongoing evolution and growth.
The major challenge is to provide the patient with a kind of therapy that is not only effective but also responds to the individual needs of the patient.
One of the main answers offered to this need is the definition of personalized therapy.

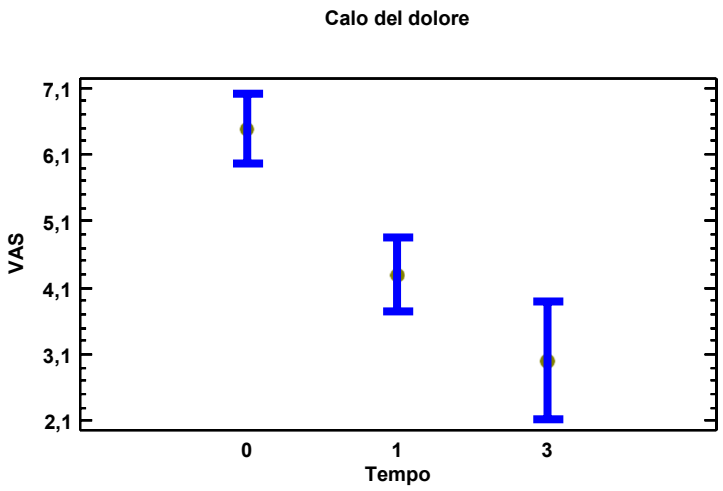
Our research about Medical Cannabis and genetic in chronic neuropathic pain, the first worldwide of the kind, it could open the way for a greater structuring of therapy on the basis of the patient individual and genetic characteristics.

Pharmacogenetic of Medical Cannabis

Altough Pharmacogenetic of Cannabis is complex and not easy to investigate, recent researches demonstrate the possible role of various genes in modulating effects of Cannabis therapy: for example, recent review describes various kind of genes and their polimorphic versions as responsible factors of benefits and adverse effects link to Cannabis therapy (1). These genes can be divided into three groups: receptors, (CNR1, CNR2, GPR55) transports,(ABCB1, SLC6A4 5-HTTLPR promoter)biotrasformator and bioactivator. (CYP3A4, CYP2C19, CYP2C9, CYP2A6,CYP1A1, COMT, FAAH, COX2, ABHD6, ABHD12 e MAPK14).
All these genes are polimorphics (single nucleotide polymorphism, SNP) and have a functional effects in human, as demonstrates by associational studies.
In this research, for every gene, it was selected a particolar SNP with funzional effects: CNR1 = rs 806380 (2), CNR2 = 2501432 (3) , GPR55 = rs 3749073 (4), ABCB1 = rs 1045642 (5) , SLC6A4 promoter rs = 2553 (6) , COMT rs= 4680 (7)

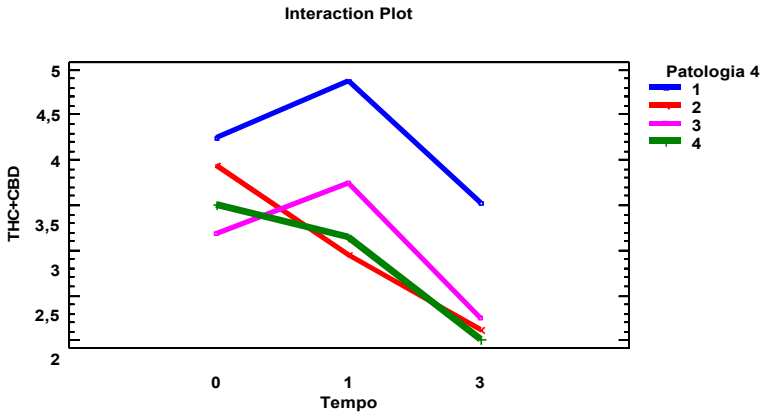
4.2 GRAPHS AND TABLES

Graph 1: Trend of Pain intensity



Graph show a significant reduction of pain intensity during 3 months of evaluation

Graph 2: Trend of THC/CBD dosages for each disease



The graph show that during the three months of evaluation the dosage of prescribed Medical Cannabis has decreased

Graph 2: Trend of Pain intensity in only Medical Cannabis group (blue line) and Medical Cannabis in addition to Opioid therapy group (red line)

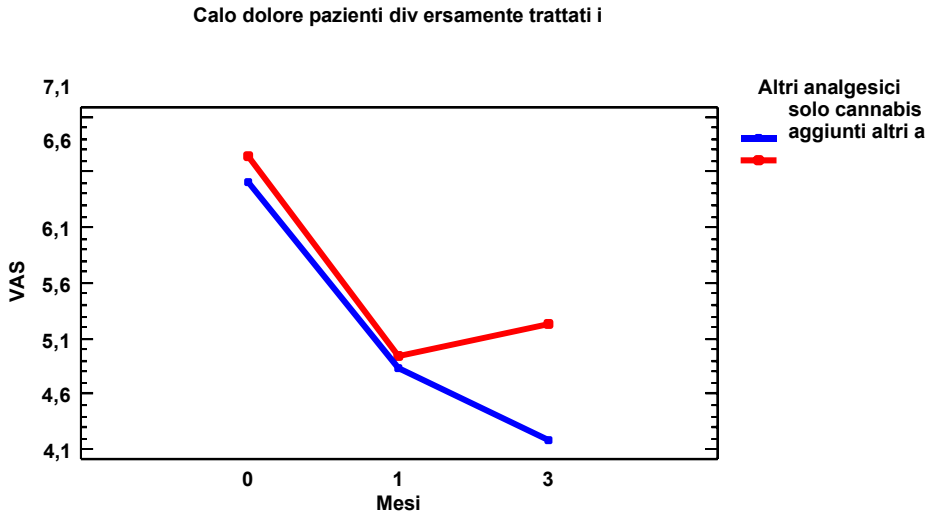


Table 1: Multifactor ANOVA of factors that exert a greater influence on pain intensity

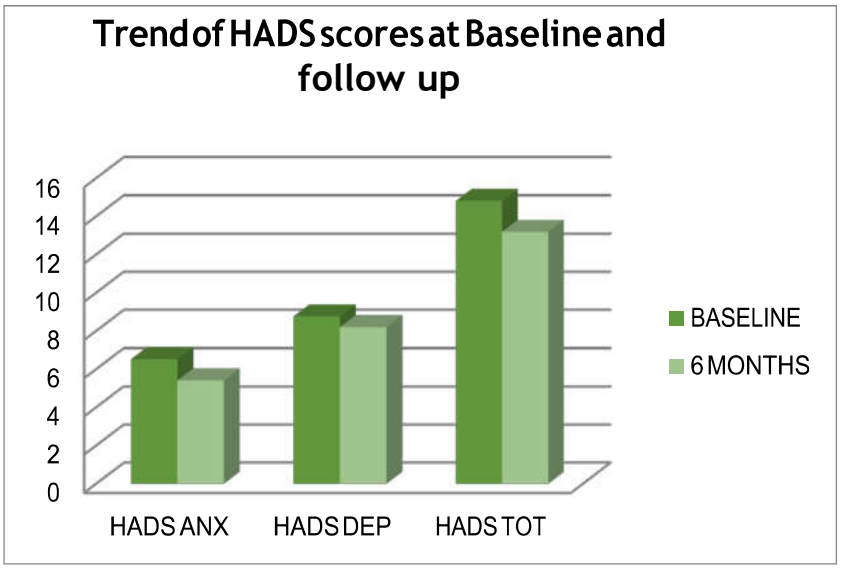
Multifactor ANOVA - VASnalysis of Variance for VAS - Type III Sums of Squares

Source	*Sum of Squares*	*Df*	*Mean Square*	*F-Ratio*	*P-Value*
COVARIATES					
TCH tot	14,6059	1	14,6059	1,83	0,1778
CBD tot	65,1894	1	65,1894	8,19	0,0049
MAIN EFFECTS					
A:Tempo	204,883	2	102,441	12,87	0,0000
B:Altri analgesici	1,91724	1	1,91724	0,24	0,6244
INTERACTIONS					
AB	4,63033	2	2,31516	0,29	0,7481
RESIDUAL	1066,6	134	7,95972		
TOTAL (CORRECTED)	1397,97	141			

All F-ratios are based on the residual mean square error.

The table show the major factors that have an influence on pain intensity: according to data reported CBD seems to be the factor that has a significant influence on pain intensity

Graph 3



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