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Long-term Cannabis-based oil therapy and pain medications prescribing patterns: an Italian observational study

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Abstract. – OBJECTIVE: Chronic pain is one of the most common medical conditions in developed countries. The 2020 Italian National Report on Medicines shows how, in the last years, there was a light but constant increase in the prescription of pain medications. The purpose of our study was to assess the effects of long-term cannabis-based oil consumption on the distribution of patients with analgesics prescriptions for chronic pain in a Pain Medicine Unit in Northern Italy.

PATIENTS AND METHODS: This is a retrospective, observational study in which patients treated with long-term medical cannabis-based oils, followed between June 2016 and July 2019, were enrolled. The effects of cannabis-based oil consumption on the distribution of patients with pain medications, before and after its long-term use, were evaluated with a Related Samples McNemar Test. Subgroups analyses were performed based on sex, age, comorbidity, duration of cannabis treatment, and condition driving cannabis prescription.

RESULTS: A significant difference in opioid non-users after a long-term cannabis-based oil therapy was identified (from 32.1% to 55.4%, $p = 0.0023$), while no significant differences were found in the distribution of anticonvulsant, antidepressant, and benzodiazepine users. A high benzodiazepine use prevalence was revealed, while subgroup analyses showed increased antidepressant use in people over 65 years old (from 93.7% to 56.2%; $p = 0.0313$).

CONCLUSIONS: Pain medication patterns of prescribing show how necessary it is to improve prescription practices among chronic pain patients. Opioid-sparing medications represent a crucial aspect of the pain treatment process, along with deprescribing protocols. Clinicians and clinical pharmacologists must cooperate to meet the need of a guide that can represent the most possible appropriate therapy for these patients.

Key Words:
Chronic pain, Medical cannabis, Marijuana treatment, Deprescribing, Opioid analgesics.

Introduction

Chronic Pain in Italy

Chronic pain is one of the most common medical conditions in developed countries. In Europe, about 19% of the adult population deals with moderate to severe chronic pain, with Italy being at third place in chronic pain prevalence[1]. Data from the 2020 National Report on Medicines use in Italy[2] shows how, in the last five years, there was a light, but constant increase in the prescription of pain medications, with a total 2020 expenditure of 396.4 million euros. However, chronic pain patients are often characterized by multimorbidity, and this condition is mostly followed by polypharmacy. In this scenario, multiple pain management and treatment guidelines have been produced, but rarely they offer an integrated approach that takes account of multimorbidity and polypharmacy in real-world chronic pain patients.

Medical Cannabis for Chronic Pain Patients

There are various pharmacological options for treating chronic pain conditions; the most commonly prescribed represented by opioid analgesics, and some medications used for neuropathic pain, represented by anticonvulsants, antidepressants, and benzodiazepines. Nevertheless, the concomitant use of these drugs is accompanied by significant risks, especially regarding the harmful consequences of seda-

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tives, such as benzodiazepines[3]. Because of the factors mentioned above, a growing body of evidence is being produced for supporting the role of cannabis in the treatment of chronic pain conditions, and the substitution of cannabis for opioid analgesics or other pain medications. However, many limits and few pieces of evidence are currently available for this indication[4-6]. Cannabis is often used as adjunctive treatment in combination with opioid analgesics and other analgesics in chronic pain conditions. Still, there is no information about possible interactions between these medication classes[7]. Cannabis is now available in different forms, from pharmaceutically prepared cannabinoids, such as dronabinol or nabilone, to plant-based cannabis preparations, such as cannabis-based oils. The first drug, based on cannabinoids, approved in Italy in 2003, has been Sativex®, an oromucosal spray, composed of two active substances, tetrahydrocannabinol (THC) and cannabidiol (CBD), extracted from the Cannabis sativa plant, for spasticity in Multiple Sclerosis when other treatments have not been effective. Moreover, the magistral preparations of cannabis-based oils are regulated by article 5 of the Decree-Law number 23 of February 1, 1998, then converted by Law number 94 of April 8, 1998. Their reimbursability, instead, is defined by Law number 172 of December 4, 2017. There are some types of active substances of plant origin consisting of inflorescences of cannabis, as Cannabis FM2 (THC 5%-8% and CBD 7,5-12%), produced by the Stabilimento Chimico Farmaceutico of Florence, and the inflorescences of cannabis imported into Italy from the Dutch Office of medicinal cannabis, defined as the Bedrocan variety (THC 19%-22% and CBD<1%), the Bediol variety (THC 6% and CBD 7.5%), and the Bedrolite variety (THC < 0.4% and CBD 9%). As regards plant-based cannabis medications, Nugent et al[8] have shown a very small difference in the mean change on visual analogue scale for chronic neuropathic pain between cannabinoids and placebo, as well as they concluded that there was not sufficient evidence to evaluate the effects of cannabinoids on pain in multiple sclerosis patients. On the other hand, a meta-analysis of patient data from 5 randomized trials[9] has shown a 3.2 odds ratio for a 30% reduction in pain, suggesting that inhaled cannabis may determine short-term relief for 1 in 5 to 6 patients with neuropathic pain, comparable to the effect of gabapentin.

Study Objectives

The purposes of our study were to assess the long-term effects of cannabis-based oil consumption on the distributions of patients with analgesics prescriptions for chronic pain, in an outpatient Pain Medicine Service at Niguarda Hospital in Northern Italy.

The primary objective of this study was to evaluate the effects of long-term cannabis-based oil consumption on the distribution of patients with an opioid prescription, within patients with a chronic pain condition, followed by the Pain Medicine Unit of Niguarda Hospital.

Secondary objectives were represented by the evaluation of the effects of long-term cannabis-based oil consumption on the distribution of patients with an anticonvulsant prescription, on the distribution of patients with an antidepressant prescription, and on the distribution of patients with a benzodiazepine or non-benzodiazepine drug prescription.

Patients and Methods

The study was approved by the Research Ethics Committee of Milan Area 3. All procedures performed were in accordance with the Ethical Standards of the Institutional Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This is a retrospective, observational study, conducted in the outpatient Pain Medicine Service at Niguarda Hospital in Northern Italy. Since this is a retrospective observational non-interventional study, it is not envisaged for possible additional risks to patients enrolled, patients to whom the best clinical care conditions were offered as part of the standard clinical practice and independently from the decision to enroll patients in the study. The reporting of this research conforms to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement checklist[10]. Data have been taken from an ongoing database gathered by Niguarda Pain Medicine Unit on medical cannabis patients. All patients aged 18 years and older, admitted to the outpatient Pain Medicine Service and prescribed cannabis-based oils for oral administration for at least six months, between June 2016 and July 2019, were recruited. The exclusion criteria were the consumption of cannabis-based products for medical use with formulations other than oil, the discontinuation of cannabis-based oil before six

months of treatment, or the lack of a follow-up visit after at least six months from the first consumption. The study provided for the retrospective evaluation of patients' medications at the visit just before the prescription of cannabis-based oil at the outpatient Pain Medicine Service, and at a follow-up visit after at least six months from the first prescription at the outpatient Pain Medicine Service. If more than one follow-up was available, we considered the last follow-up visit in terms of time. If inclusion criteria were fulfilled, individual participants' data, including age, sex, primary diagnosis for cannabis-based oil prescription, comorbidity level, both basal and follow-up number of prescribed medications, both basal and follow-up anticonvulsant, antidepressant and benzodiazepine and non-benzodiazepine drugs use, were recorded. The primary diagnoses for cannabis-based oil prescription were distributed in two categories, defined as chronic pain conditions, and chronic spasticity conditions with pain. In this last category have been collected multiple sclerosis and spinal cord injuries, while in the first category have been grouped all the other chronic pain conditions. Daily Morphine Milligram Equivalents doses for commonly prescribed opioid analgesics and daily diazepam milligram equivalents doses were calculated based on guidance, and resources for tapering, collected and developed by the Oregon Pain Guidance Clinical Advisory Group[11]. Long-term cannabis-based oil consumption was defined as the consumption of cannabis for at least six consecutive months. Polypharmacy was defined as five or more medications prescribed[12]. Comorbidity was measured by means of the Charlson comorbidity index (CCI)[13]. The severity of comorbidity level was classified into two grades, defined as non-severe (CCI < 5), and as severe (CCI ≥ 5). The sample size was defined based on estimated prevalence, from a previous study[14], and from an internal analysis, of patients in which opioid analgesics were discontinued after the introduction of a cannabis-based therapy. Proposing that 70% and 35% of the pairs would be given opioid analgesics before the prescription of cannabis-based oil and after the prescription of cannabis-based oil, respectively, the predetermined sample size was 37 patients for the study, to achieve a power of 80% and a two-sided significance of 5% for detecting a difference of 0.35 between marginal proportions[15]. All data needed to compute statistical analysis were regularly collected and entered into the database anonymously.

Statistical Analysis

Descriptive statistics were used to introduce the data. Frequency and percentage were calculated for dichotomous and categorical variables (sex, older adults, diagnosis, comorbidities, basal polypharmacy, and follow-up polypharmacy), while continuous variables (age, basal number of pain medications, follow-up number of pain medications, duration of medical cannabis consumption, number of follow-up visits) were presented as median values along with interquartile range (IQR) as the measure of dispersion.

A Related-Samples McNemar Test was performed for evaluating the effects of long-term cannabis-based oil consumption on the distribution of patients with an opioid prescription, as well as on the distribution of patients with an anticonvulsant prescription, on the distribution of patients with an antidepressant prescription, and on the distribution of patients with a benzodiazepine prescription. Subgroups analyses were performed based on sex, age, comorbidity, duration of cannabis treatment, and condition driving cannabis treatment prescription. The statistical analyses were performed using IBM SPSS Statistics for Windows (version 20; Armonk, NY, USA). The significance level was set at $p < 0.05$.

Results

During the considered period, 186 patients were prescribed cannabis-based oil for a pain-related disorder within the outpatient Pain Therapy Service at Niguarda Hospital. Data were retrospectively collected from 56 consecutive subjects, who met the inclusion criteria. We excluded 130 patients for the following reasons: different formulations (6 patients), discontinuation of cannabis-based oil before six months (20 patients), and lack of a follow-up visit after at least six months from the first consumption (104 patients). Of the final sample of 56 patients, 41 (73.2%) were female (Table I). The median age (IQR) was 57 (44-67) years, with 28.6% of people aged 65 years or older. The most prevalent diagnoses driving medical cannabis prescription were fibromyalgia (37.5% of patients) and failed back surgery syndrome (12.5% of patients). The median duration (IQR) of cannabis-based oil consumption was 12 (8-21) months, with 28 patients (50%) consuming it for more than one year, while the median number (IQR) of follow-up visits after cannabis-based oil prescription was 4

Table I. Characteristics of the Study Sample (N = 56).

Characteristic	Value
Sex, n (%)	
Female	41 (73.2)
Male	15 (26.8)
Age, median (IQR)	57 (44-67)
< 65, n (%)	40 (71.4)
≥ 65, n (%)	16 (28.6)
Primary diagnosis, n (%)	
Fibromyalgia	21 (37.5)
Failed Back Surgery Syndrome	7 (12.5)
Multiple sclerosis	3 (5.3)
Postherpetic polyneuropathy	2 (3.6)
Other	23 (41.1)
Comorbidity, n (%)	
Non-severe	48 (85.7)
Severe	8 (14.3)
Polypharmacy before cannabis-based oil prescription, n (%)	33 (58.9)
Polypharmacy at follow-up visit, n (%)	33 (58.9)
Number of total medications before cannabis-based oil prescription, median (IQR)	6 (3-7)
Number of total medications at follow-up visit, median (IQR)	6 (3-8)
Number of pain medications before cannabis-based oil prescription, median (IQR)	2 (1-3)
Number of pain medications at follow-up visit, median (IQR)	2 (1-3)
Number of follow-up visits after cannabis-based oil prescription, median (IQR)	4 (3-6)
Duration of cannabis-based oil assumption, median (IQR)	12 (8-21)
≤ 12 months, n (%)	28 (50)
> 12 months, n (%)	28 (50)
Type of cannabis-based oil, n (%)	
Bedrocan	44 (78.5)
Bediol	10 (17.9)
FM2	2 (3.6)

Definitions and abbreviations. Percentage values are rounded up to 1 decimal. N, number of patients; IQR, interquartile range; Comorbidity, measured by means of Charlson Comorbidity Index[13]. Severity of comorbidity level: non-severe (Charlson Comorbidity Index < 5), severe (Charlson Comorbidity Index ≥ 5). Polypharmacy, defined as 5 or more medications prescribed[12].

(3-6). The median number (IQR) of medications, including pain drugs, before cannabis-based oil prescription, was 6 (3-7), with 58.9% of patients receiving polypharmacy, while the median number (IQR) of pain medications only, before cannabis-based oil prescription, was 2 (1-3). The median number (IQR) of medications, including pain drugs, at the follow-up visit, was 6 (3-8), with 58.9% of patients receiving polypharmacy, while the median number (IQR) of pain medications only, at the follow-up visit, was 2 (1-3). The most prevalent cannabis-based oil prescribed was Bedrocan (78.5% of patients), followed by Bediol (17.9% of patients), and by FM2 (3.6% of patients). The main characteristics of the study sample are shown in Table I.

Use of Opioid Analgesics Before and After Cannabis-Based Oil Treatment

Around-the-clock opioid analgesic use was recorded in 38 patients (67.9%) before the first cannabis-based oil prescription. The most commonly prescribed opioid analgesic was oral oxycodone (9/38, 23.7% of opioid users), alone (3/38) or in combination with naloxone (6/38), followed by transdermal buprenorphine (7/38, 18.4% of opioid users). Daily Morphine Milligram Equivalents doses of 90 or more were recorded in 8 patients (21% of opioid users). An as-needed opioid therapy was prescribed in 32 out of the 56 patients (57.1%). Of these 32 patients, 26 subjects were prescribed an around-the-clock opioid analgesic, while 6 patients were not (Table II).

Around-the-clock opioid analgesic use was recorded in 25 patients (44.6%) at the last follow-up visit after a cannabis-based oil prescription. The most commonly prescribed opioid analgesic was oral oxycodone (7/25, 28% of opioid users), alone (2/25) or in combination with naloxone (5/25), followed by oral hydromorphone (6/25, 24% of opioid users). Daily Morphine Milligram Equiva-

Table II. Association of circ_001680 expression with clinicopathologic characteristics of glioma.

Characteristic	Value	
	Before cannabis treatment	≥ 6 month cannabis treatment
Around-The-Clock Opioid medications, n (%)	38 (67.9%)	25 (44.6)
Oral Hydromorphone	4 (7.1)	6 (10.7)
Oral Morphine Sulfate	1 (1.9)	0
Oral Methadone	2 (3.6)	3 (5.3)
Oral Oxycodone	9 (16.1)	7 (12.5)
Oral Tapentadol	4 (7.1)	3 (5.3)
Oral Tramadol	4 (7.1)	1 (1.9)
Transdermal Buprenorphine	7 (12.5)	5 (8.9)
Transdermal Fentanyl	4 (7.1)	0
Daily Morphine Milligram Equivalents, median (IQR)	36 (12-67)	40 (15-60)
< 90, n (%)	30 (53.6)	21 (37.5)
≥ 90, n (%)	8 (14.3)	4 (7.1)
As-needed opioid therapy, n (%)	32 (57.1)	32 (57.1)
Patients with an around-the-clock opioid medication	26 (46.4)	18 (32.1)
Patients without an around-the-clock opioid medication	6 (10.7)	14 (25)
Anticonvulsant therapy, n (%)	24 (42.8)	19 (33.9)
Gabapentin	9 (16.1)	6 (10.7)
Lamotrigine	0	1 (1.9)
Oxcarbazepine	1 (1.9)	0
Pregabalin	14 (25.0)	12 (21.4)
Antidepressant therapy, n (%)	18 (32.1)	22 (39.3)
S-Adenosyl methionine	1 (1.9)	0
Serotonin Norepinephrine Reuptake Inhibitor	9 (16.1)	12 (21.4)
Selective Serotonin Reuptake Inhibitor	4 (7.1)	6 (10.7)
Tricyclic Antidepressant	4 (7.1)	4 (7.1)
Benzodiazepines and non-benzodiazepine drugs, n (%)	30 (53.6)	29 (51.8)
Alprazolam	4 (7.1)	5 (8.9)
Clonazepam	18 (32.1)	17 (28.6)
Delorazepam	2 (3.6)	2 (3.6)
Diazepam	1 (1.9)	1 (1.9)
Lorazepam	2 (3.6)	2 (3.6)
Prazepam	1 (1.9)	1 (1.9)
Zolpidem	2 (3.6)	2 (3.6)
Daily diazepam milligram equivalents, median (IQR)	10 (10-16)	10 (10-16)

Definitions and abbreviations. Percentage values are rounded up to 1 decimal. N, number of patients; IQR, interquartile range. Around-The-Clock medication, defined as medication that is given at regularly scheduled intervals throughout the day. As-needed therapy, defined as medication that is used only when needed for a specific situation, as pain.

lents doses of 90 or more were recorded in 4 patients (16% of opioid users). An as-needed opioid therapy was prescribed in 18 out of the 25 opioid users (72%), while in 6 patients the as-needed treatment was represented by a non-opioid medication (Table II).

Of the 56 patients recruited, before the prescription of cannabis-based oil, 18 subjects (32.1%) were opioid non-users. After at least six months of cannabis-based oil consumption, the number of opioid non-users had increased to 31 patients (55.4%), with a concomitant reduction in the number of opioid users to 25 participants (44.6%). This change resulted from 15 opioid users' pre-medical cannabis consumption, becoming opioid non-users post-medical cannabis consumption, but with two participants who were initially opioid non-users becoming opioid users after cannabis prescription. An exact McNemar's test determined that this difference in the proportion of opioid non-users from a pre-consumption value of 32.1% to 55.4% post-medical cannabis consumption was statistically significant, $p = 0.0023$ (Table III).

Analyses by subgroups showed a statistically significant difference in the proportion of female opioid non-users before and after cannabis-based oil treatment (34.1% to 56.1%; $p =$

Table III. Use of opioids and other pain medications before and after 6-month cannabis-based oil treatment by groups (sex, age, comorbidity, duration of cannabis-based oil treatment, and condition driving cannabis treatment prescription) (N = 56).

	Group →	**Sex**		**Age**		**Comorbidity**		**Duration of cannabis**		**Condition driving cannabis prescription**	
	Subgroup →	Female	Male	<65 y	≥65 y	Non-severe	Severe	≤12 m	>12 m	Chronic pain conditions	Chronic spasticity conditions with pain
Number of patients →	**56**	41	15	40	16	48	8	28	28	49	7
Opioid non-users, n (%)											
Before cannabis treatment	18 (32.1)	14 (34.1)	4 (26.7)	13 (32.5)	5 (31.2)	16 (33.3)	2 (25)	15 (53.6)	3 (10.7)	16 (32.6)	2 (28.6)
≥6 month cannabis treatment	31 (55.3)	23 (56.1)	8 (53.3)	22 (55)	9 (56.2)	26 (54.2)	5 (62.5)	20 (71.4)	11 (39.3)	29 (59.2)	2 (28.6)
Significance of difference, p	*0.0023*	*0.0225*	*0.1250*	*0.0225*	*0.1250*	*0.0129*	*0.2500*	*0.1797*	*0.0078*	*0.0010*	*1.000*
Anticonvulsant non-users, n (%)											
Before cannabis treatment	32 (57.1)	23 (56.1)	9 (60)	21 (52.5)	11 (68.7)	26 (54.2)	6 (75)	19 (67.9)	13 (46.4)	30 (61.2)	2 (28.6)
≥6 month cannabis treatment	37 (66.1)	28 (68.3)	9 (60)	27 (67.5)	10 (62.5)	32 (66.7)	5 (62.5)	13 (46.4)	24 (85.7)	30 (61.2)	0
Significance of difference, p	*0.4410*	*0.3833*	*1.000*	*0.2630*	*1.000*	*0.3075*	*1.000*	*0.1796*	*0.0034*	*1.000*	*0.0625*
Antidepressant non-users, n (%)											
Before cannabis treatment	38 (67.9)	28 (68.3)	10 (66.7)	23 (57.5)	15 (93.7)	32 (66.7)	6 (75)	21 (75)	17 (60.7)	34 (69.4)	4 (57.1)
≥6 month cannabis treatment	34 (60.7)	25 (61)	9 (60)	25 (62.5)	9 (56.2)	30 (62.5)	4 (50)	14 (50)	20 (71.4)	28 (57.1)	6 (85.7)
Significance of difference, p	*0.5413*	*0.6291*	*1.000*	*0.8145*	*0.0313*	*0.8238*	*0.6250*	*0.0923*	*0.5488*	*0.2632*	*0.6250*
Benzodiazepine non-users, n (%)											
Before cannabis treatment	26 (46.4)	21 (51.2)	5 (33.3)	19 (47.5)	7 (43.7)	23 (47.9)	3 (37.5)	13 (46.4)	13 (46.4)	21 (42.9)	5 (71.4)
≥6 month cannabis treatment	27 (48.2)	21 (51.2)	6 (40)	19 (47.5)	8 (50)	23 (47.9)	4 (50)	11 (39.3)	16 (57.1)	21 (42.9)	6 (85.7)
Significance of difference, p	*1.000*	*1.000*	*1.000*	*1.000*	*1.000*	*1.000*	*1.000*	*0.6250*	*0.4531*	*1.000*	*1.000*

Definitions and abbreviations. Percentage values are rounded up to 1 decimal. n, number of patients; y, years; m, months; Comorbidity, measured by means of Charlson Comorbidity Index 13. Severity of comorbidity level: non-severe (Charlson Comorbidity Index < 5), severe (Charlson Comorbidity Index ≥ 5). Chronic spasticity conditions with pain include multiple sclerosis and spinal cord injuries diagnoses. Non-users, defined as patients who were not receiving the medication. Statistical analyses were performed using IBM SPSS Statistics for Windows (version 20; Armonk, New York). The significance level is 0.05.

0.0225), as well as in the proportion of under-65 years old opioid non-users before and after cannabis-based oil treatment (32.5% to 55%; p = 0.0225), in the proportion of opioid non-users with non-severe comorbidity (33.3% to 54.2%; p = 0.0129), in the proportion of opioid non-users with a duration of cannabis-based oil of more than 12 months (10.7% to 39.3%; p = 0.0078), and in the proportion of opioid non-users with a chronic pain condition (32.6% to 59.2%; p = 0.001) (Table III).

Use Of Anticonvulsant Medications Before and After Cannabis-Based Oil Treatment

Anticonvulsant medication use was recorded in 24 patients (42.8%) before the first cannabis-based oil prescription. The most commonly prescribed anticonvulsant drug was pregabalin (14/24, 58.3% of anticonvulsant users), followed by gabapentin (9/24, 37.5% of anticonvulsant users) (Table II).

Anticonvulsant medication use was recorded in 19 patients (33.9%) at the last follow-up visit after a cannabis-based oil prescription. The most commonly prescribed anticonvulsant drug was pregabalin (12/19, 63.1% of anticonvulsant users), followed by gabapentin (6/19, 31.6% of anticonvulsant users) (Table II).

Of the 56 patients recruited, before the prescription of cannabis-based oil, 32 subjects (57.1%) were anticonvulsant drug non-users. After at least six months of cannabis-based oil consumption, the number of anticonvulsant drug non-users increased to 37 patients (66.1%) with a concomitant reduction in the number of anticonvulsant drug users to 19 participants (33.9%). This change was a consequence of 16 anticonvulsant drug users pre-medical cannabis consumption, becoming anticonvulsant drug non-users post-medical cannabis consumption, but with 11 participants who were initially anticonvulsant drug non-users becoming anticonvulsant drug users after cannabis prescription. A McNemar's test with continuity correction determined that the difference in the proportion of anticonvulsant drug non-users pre- and post-cannabis-based oil treatment was not statistically significant, $\chi^2(1)$ = 0.593, p = 0.441. Analyses by subgroups showed a statistically significant difference in the proportion of anticonvulsant drug non-users with a duration of cannabis-based oil of more than 12 months (46.4% to 85.7%; p = 0.003) (Table III).

Use of Antidepressant Medications Before and After Cannabis-Based Oil Treatment

Antidepressant medication use was recorded in 18 patients (32.1%) before the first cannabis-based oil prescription. The most commonly prescribed class of antidepressant drug was Serotonin Norepinephrine Reuptake Inhibitors (9/18, 50% of antidepressant users), followed by Tricyclic antidepressants (4/18, 22.2% of antidepressant users), and by Selective Serotonin Reuptake Inhibitors (4/18, 22.2% of antidepressant users) (Table II).

Antidepressant medication use was recorded in 22 patients (39.3%) at the last follow-up visit after a cannabis-based oil prescription. The most commonly prescribed class of antidepressant drug was Serotonin Norepinephrine Reuptake Inhibitors (12/22, 54.5% of antidepressant users), followed by Selective Serotonin Reuptake Inhibitors (6/22, 27.3% of antidepressant users), and by Tricyclic antidepressants (4/22, 18.2% of antidepressant users) (Table II).

Of the 56 patients recruited, before the prescription of cannabis-based oil, 38 subjects (67.9%) were antidepressant non-users. After at least six months of cannabis-based oil consumption, the number of antidepressant non-users decreased to 34 patients (60.7%) with a concomitant increment in the number of antidepressant users to 22 participants (39.3%). This change was a consequence of 10 antidepressant users pre-medical cannabis consumption, becoming antidepressant non-users post-medical cannabis consumption, but with 14 participants who were initially antidepressant non-users becoming antidepressant users after cannabis prescription. An exact McNemar's test determined that this difference in the proportion of antidepressant non-users from a pre-consumption value of 67.9% to 60.7% post-medical cannabis consumption was not statistically significant, $p = 0.5413$.

Analyses by subgroups showed a statistically significant difference in the proportion of over-65 years old antidepressant non-users before and after cannabis-based oil treatment (93.7% to 56.2%; $p = 0.0313$) (Table III).

Use of benzodiazepine and non-benzodiazepine medications before and after cannabis-based oil treatment

Benzodiazepine and non-benzodiazepine drug use were recorded in 30 patients (53.6%) before the first cannabis-based oil prescription. The most commonly prescribed benzodiazepine was oral clonazepam (18/30, 60% of benzodiazepine users), while the median (IQR) daily diazepam milligram equivalents dose was 10 (10-16) (Table II).

Benzodiazepine and non-benzodiazepine drug use were recorded in 29 patients (51.8%) at the last follow-up visit after a cannabis-based oil prescription. The most commonly prescribed benzodiazepine was oral clonazepam (17/29, 58.6% of benzodiazepine users), with a patient prescribed with both clonazepam 1.5 mg and diazepam 10 mg. The median (IQR) daily diazepam milligram equivalents dose was 10 (10-16) (Table II).

Of the 56 patients recruited, before the prescription of cannabis-based oil, 26 subjects (46.4%) were benzodiazepine non-users. After at least six months of cannabis-based oil consumption, the number of benzodiazepine non-users increased of one patient, to 27 (48.2%) with a concomitant reduction in the number of benzodiazepine users to 29 participants (51.8%). This change was a consequence of 6 benzodiazepine users pre-medical cannabis consumption, becoming benzodiazepine non-user post-medical cannabis consumption, but with 5 participants who were initially benzodiazepine non-users becoming benzodiazepine users after cannabis prescription. An exact McNemar's test determined that this difference in the proportion of benzodiazepine non-users from a pre-consumption value of 46.4% to 48.2% post-medical cannabis consumption was not statistically significant, $p = 1.000$, as well as analyses by subgroups did not show statistically significant differences (Table III).

Discussion

This study investigates how cannabis-based medical products might determine an effect on pain medication prescribing in patients followed by a Pain Medicine Unit of an Italian hospital. To the best of our knowledge, this is the first study that examines these effects on opioid analgesics use distribution, as well as on anticonvulsant, antidepressant and benzodiazepine use distributions, in an Italian setting. First of all, patients followed by our Pain Medicine Unit are represented by a middle-aged population, of which more than half with five or more medications prescribed, both before and after cannabis-based oil treatment. In this scenario, we found a significant increase in the number of opioid non-users (+23.3% of patients without an opioid-based therapy) from the start of cannabis-based oil treatment to the last follow-up

visit at the Pain Medicine Unit. Only two patients who were initially opioid non-users had been prescribed an opioid analgesic after cannabis-based treatment, because of exacerbation of basal disease and no pain relief reported, respectively. Another interesting point in our study was represented by the median daily morphine milligram equivalents doses prescribed in this population, that remained stable after the introduction of a cannabis-based treatment, ranging from 36 to 40 milligrams, but with a decrease from ten to three in the number of patients with less than 20 daily milligrams at the follow-up visit. In our study, the increase in the number of opioid non-users was also significant in subanalyses, including the female group, people under 65 years, without severe comorbidity, and with a duration of cannabis-based treatment of more than one year. This is consistent with findings from previous studies[16], because a younger age, fewer comorbidities, fewer medications, and a longer-lasting and more structured treatment make us believe that medication discontinuation or reduction might be more feasible. Furthermore, as above-mentioned, our population included about 30 percent of people over 65 years of age, of which approximately 70 percent before, and 40 percent after at least six months of cannabis-based treatment, were prescribed with an opioid analgesic. Opioid analgesic use among older adults may result in several side effects, such as constipation, excessive sedation, impaired vision, as well as impaired attention, coordination, and subsequent increased risk of falls[17]. These findings suggest that an improvement in the prescription of opioid analgesics is needed, as recommended by international guidelines, as the CDC Guideline for Prescribing Opioids for Chronic Pain[18]. Several documents and toolkit[3,18-22] are now available for tackling opioid use in long-term prescriptions, with deprescribing protocols being one of the best possible strategies to reverse the harms of analgesic medications. Patient-specific deprescribing interventions may reduce risks of severe harm related to opioid therapy, especially in older adult patients with polypharmacy, in which deprescribing could be achieved without negative outcomes in quality of life[23]. On the other hand, as previously described in the introductive chapter, using combinations of drugs with complementary mechanisms may maximize the antalgic effects, leading to a reduction of the doses of each medication, and consequently reducing the risk for opioid overuse or overdose. In the search for these opioid-sparing medications, considering specific properties of the endocannabinoid system, such as the similarity of signal transduction systems between opioids and cannabinoids, as well as the co-localization of opioid receptors and cannabinoid receptors in the spinal cord, some studies[24-25] have suggested that cannabinoid medications may have this opioid-sparing potential. On the other hand, a systematic review[26] of 9 controlled clinical studies on the opioid-sparing effect of cannabinoids showed some beneficial consequences of the coadministration of cannabinoid and opioid on pain, sleep, and performance in chronic pain participants. One observational research[14] has found a reduction by up to more than 60% in opioid consumption in chronic pain patients prescribed with medical cannabis, while a case series of chronic non-cancer pain patients described a decrease in opioid doses after smoked cannabis[27]. In this trend, our study seems to be aligned with previous researches, if we consider the reduction of opioid use in terms of the number of patients.

As regards anticonvulsant and antidepressant medications, our evaluation did not make explicit any significant sparing effect from long-term treatment with cannabis-based oil. However, we found a significant reduction in the proportion of older adults not prescribed an antidepressant medication after at least 6-month consumption of medical cannabis. Several reviews and international guidelines[28-31] have pointed out that antidepressants, such as tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors, are effective analgesics in chronic neuropathic pain and fibromyalgia, but it is also known that, especially tricyclic antidepressants, are associated with clinically significant anticholinergic activity, to which older adults are particularly sensitive[32]. Although longitudinal studies suggest long-term recreational cannabis use is associated with an increase of depressive symptoms[33], it is still difficult to confirm a causal association. Additionally, according to Whiting et al[34], there was no evidence for a difference in the association of cannabinoids with the incidence of depression, even if none of the included studies evaluated long-term adverse events of cannabinoids. Consequently, we think that some elements might get involved in this result, as the chronic use of antidepressants also for indications other than chronic pain, such as anxiety, and depression, with subsequent discontinuation after the prescription of an additional drug like cannabis, in an already polypharmacy population, as well as it may be due to the small sample size, and the

different purpose of the study, lacking power to detect this prescribing pattern.

Another critical issue among patients with chronic pain conditions is represented by the prescription of benzodiazepines or so-called Z-drugs, frequently in combination with opioid analgesics or other sedative effect medications. Unlike a previous study[6], our data do not suggest any reduction in benzodiazepine use after at least six months of medical cannabis, with clonazepam being the most common drug prescribed, as in Cunningham et al[35] study. Although clonazepam may have an antagonizing effect on hyperexcitability of neurotransmission through the GABAergic pathways, a Cochrane review[36] underlined no evidence to support the use of this benzodiazepine for chronic pain. Available studies[37-40] on the association of benzodiazepines and opioid analgesics show contrasting results for adverse events, but with the suggestion of a potential enhancement of the risk of cognitive effects, falls, and drug-related death. In addition, benzodiazepines, as well as antidepressant medications, may cause or exacerbate electrolyte disturbances, like hyponatremia, or a syndrome of inappropriate antidiuretic hormone secretion, by requiring particular attention in older adults prescription[32].

Pain medication patterns of prescribing here introduced show how necessary it is to improve prescribing practices among chronic pain patients. Opioid-sparing medications represent a key aspect of the pain treatment process. Cannabis might be an effective treatment for chronic pain in adults[34,41], and the oral consumption of cannabinoids in oil rules out the potential risk for respiratory diseases. Chronic pain pharmacological approaches can be performed in various ways, involving different medication classes, with different risk profiles, and potential positive and negative interactions. We should also consider that, in this complex frame, physicians are supposed to manage the difference between appropriate polypharmacy and too many drugs, choosing the best interventions aimed at reducing the iatrogenic risk as much as possible. To guide clinicians in the best possible appropriate treatments, opioid-sparing medications may be associated with deprescribing protocols, and with an evaluation of the overall risk of drug-induced harm in individual patients.

Despite all the evaluations of pain therapy prescribing discussed above, we have to underline some important limitations of our research: first, this is a retrospective single-center study, with a small study sample compared to other researches, not able to detect a causative association between cannabis-based medicines and pain drugs in chronic pain patients, together with the choice of groups in order to reduce confounding. Indeed, our evaluations may have been affected by the lack of cannabinoid doses in terms of milligrams per milliliter, as they were not available from the cannabis database. Consequently, it was not possible to determine if different doses of tetrahydrocannabinol or cannabidiol might differentiate the distribution of pain medication use among the study sample. Second, we focus only on the distribution of patients related to medication use, but the impact of cannabis-based oil treatment on clinical outcomes, such as pain relief, enjoyment of life, and general activities need to be assessed in future research.

Conclusions

This study provides insights into the prescribing patterns of pain medications of an Italian outpatient Pain Medicine Service. A significant increase in the number of opioid non-users after at least 6-month cannabis-based oil therapy was found, while this effect was not shown for anticonvulsant, antidepressant, and benzodiazepine medications. A significant reduction in the proportion of older adults did not prescribe an antidepressant medication was found. This study is important to raise awareness of the potential long-term effect of an oral formulation of medical cannabis on a chronic pain population. Clinicians and clinical pharmacologists must join forces in order to answer the necessity of a guide to the best possible appropriate therapy for patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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