Multiple Sclerosis and Related Disorders 48 (2021) 102708

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Original article

Safety and efficacy of low-dose medical cannabis oils in multiple sclerosis

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A B S T A C T

Introduction: The use of cannabis as medical therapy to treat chronic pain and spasticity in patients with multiple sclerosis (MS) is increasing. However, the evidence on safety when initiating treatment with medical cannabis oils is limited. The aim of this study was to investigate the safety of sublingual medical cannabis oils in patients with MS.

Methods: In this prospective observational safety study 28 patients with MS were treated with medical cannabis oils (THC-rich, CBD-rich and THC+CBD combined products) and were followed during a titration period of four weeks. Patients were evaluated at treatment start (Visit 1) and after four weeks treatment (Visit 2). At each visit neurological examination (Expanded Disability Status Scale – EDSS), ambulation (Timed 25-Foot Walk Test - T25FWT), routine blood tests, plasma cannabinoids, dexterity (9-Hole Peg Test - 9-HPT) and processing speed (Symbol Digit Modalities Test - SDMT) were tested. Adverse events (AEs) and tolerability were reported at Visit 2. Secondary, efficacy of medical cannabis on pain, spasticity and sleep disturbances were measured by numeric rating scale (NRS-11) each day during the 4-week treatment period.

Results: During treatment with cannabis preparations containing 10-25 mg/mL THC, the most common AEs were dry mouth, drowsiness, dizziness and nausea of mild to moderate degree. Two patients experienced pronounced symptoms with excessive dreaming and drowsiness, respectively, which led to treatment stop during the titration. Three serious adverse events (SAE) were reported but were not associated with the treatment. Mean doses of THC and CBD were 4.0 mg and 7.0 mg, respectively, and primarily administered as a once-daily evening dose. Furthermore, pain decreased from a median NRS score of 7 to 4, ($p = 0.01$), spasticity decreased from a median NRS score of 6 to 2.5 ($p = 0.01$) and sleep disturbances decreased from a median NRS score of 7 to 3 ($p < 0.001$). No impairment in disability, ambulation, dexterity or processing speed was observed.

Conclusion: Treatment with medical cannabis oils was safe and well tolerated, and resulted in a reduction in pain intensity, spasticity and sleep disturbances in MS patients. This suggests that medical cannabis oils can be used safely, especially at relatively low doses and with slow titration, as an alternative to treat MS-related symptoms when conventional therapy is inadequate.

1. Introduction

Multiple sclerosis (MS) is an immune-mediated neurological disease. A malfunction of the immune system causes destruction of myelin sheets and axons in the central nervous system. MS is the most frequent neurological disease leading to prolonged and progressive physical, psychological and cognitive disability in young adults. With a prevalence of 284/100.000 Denmark has one of the highest prevalence of MS in the world. (The Danish Multiple Sclerosis Registry, 2020) Chronic central neuropathic pain and spasticity are both pronounced symptoms seen among 63% and 80% of people with MS, respectively. (Foley et al., 2013), (Bethoux and Marrie, 2016) Over the last decades cannabis has been suggested as a new treatment option for chronic pain and spasticity.

The cannabis plant, *cannabis sativa*, produces unique compounds called cannabinoids. (Andre et al., 2016) The predominant compounds are tetrahydrocannabinol (THC), which is psychotropic, and cannabidiol (CBD), which is non-psychotropic. The biological effects of cannabinoids rely on their interaction with the endogenous cannabinoid system (ECS), an important system in modulating and controlling neurotransmitters and immune system activity. (Ullrich et al., 2007) Comprehensive reviews and international guidelines on the efficacy of cannabis-based medicine to alleviate neuropathic pain and spasticity have inconsistent conclusions. (NICE Guidelines, 2019, National Academies of Sciences, Engineering, and Medicine 2017, Mücke et al., 2018) However, a recent systematic review of reviews concluded that cannabinoids may have modest effect in MS in the management of pain and spasticity. (Nielsen et al., 2018)

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https://doi.org/10.1016/j.msard.2020.102708
Received 15 September 2020; Received in revised form 30 November 2020; Accepted 17 December 2020
Available online 30 December 2020

The acceptance of cannabis as medical therapy to treat chronic pain and spasticity in patients with MS is increasing. In Denmark, cannabis-based medicine includes THC and CBD isolates, synthetic THC (Marinol®), and THC/CBD extract (nabiximols or Sativex®). All products require a prescription, which is a rigorous process. Therefore, only a small fraction of MS patients are treated with cannabis-based medicine. However, patients with MS in Denmark (and many other countries) are aware of the potential beneficial effects of cannabis; therefore, cannabis products are primarily acquired illegally. (Gustavsen et al., 2019)

To unravel this controversy, the Danish government has approved a four-year *'medical cannabis pilot program'* that allows doctors to prescribe medical cannabis products to selected patient groups, which, before now, has been illegal in Denmark (The Danish Ministry of Health, 2018). Medical indications in this program include four groups: nausea after chemotherapy, chronic neuropathic pain, painful spasms caused by MS and painful spasms caused by spinal cord damage. The products are not approved medical products, have usually not been tested in clinical trials and contain no package leaflet or dosage recommendations. The *'medical cannabis pilot program'* became effective January 1, 2018, and included medical cannabis 'flos' (whole, dried female flower) and oils.

To our knowledge, no clinical studies have investigated the safety of medical cannabis oils in MS. Therefore, we aimed to examine the safety and titration of sublingual medical cannabis oils among patients with MS.

2. Material and methods

2.1. Study participants and enrollment

Under the umbrella of the national *'medical cannabis pilot program'* medical cannabis treatment could be offered to patients diagnosed with MS, who suffered from refractory neuropathic pain and/or spasticity. In addition, if patients suffered from both pain and spasticity, medical cannabis treatment could be initiated if 1-2 conventional analgesic and antispasmodic drugs have been tried without sufficient effect. Patients were enrolled in the present local project from January 2019 to April 2020 at the Danish Multiple Sclerosis Center, Copenhagen University Hospital. Patients were 18 years or older, had to pay for the medication and were recommended not to drive during the treatment. All patients signed informed consent.

Patients initiated treatment in accordance with the guidelines for doctors on the medical cannabis pilot program prepared by the Danish Medicines Agency. (Danish Medicines Agency, 2018) The guidelines are not considered actual treatment guides and do not include product-specific information or dosage recommendations. National guideline recommendations on pharmacological management of neuropathic pain included tricyclic antidepressants (TCA), anticonvulsants, serotonin-norepinephrine reuptake inhibitors (SNRI), weak and strong opioids. (National Treatment Guidelines, 2020) In regard of antispasmodic treatment, conventional oral treatment included baclofen, tizanidine, benzodiazepines, gabapentin and nabiximols (Sativex®). (National Treatment Guidelines, 2020). The medical cannabis oils were administered as add-on therapy. THC and CBD combined preparations were recommended at treatment start due to the comparability to the regulatory approved and well-studied cannabis extract drug nabiximols (Sativex®). CBD-rich treatment was indicated if patients previously had experienced unacceptable side effects of THC products or were dependent on being able to drive a car.

Exclusion criteria were as follows: history of major psychiatric disorder other than depression; history of substance abuse; unstable medical illnesses including heart, liver or kidney disease; breastfeeding; pregnancy; and known allergy to cannabinoids.

2.2. Definitions

Medical cannabis is a wide-ranging term. In this study medical cannabis is defined as cannabis products containing not only plant derived cannabinoids but also other organic compounds from the cannabis plant, e.g. terpenes. Products consisting of isolates or synthetic cannabinoids without other organic compounds are defined as cannabis-based products (e.g. THC and CBD isolates, Marinol and Nabilone).

Full-spectrum cannabis extracts contain many of the cannabinoids and terpenes found in the original plant, and broad-spectrum products contain multiple cannabinoids found in the plant; however, broad-spectrum products are lacking some of the other organic compounds.

2.3. Cannabis preparations

At study initiation three full spectrum oils were included in the pilot program. The products included: THC DROPS (25 mg THC, <2 mg CBD/mL), CBD DROPS (25 mg CBD, 2 mg THC/mL) and 1:1 DROPS (12.5 mg THC and CBD/mL) from the company STENOCARE, Denmark. Unfortunately, 6 months after study initiation the supplier of the three full-spectrum oils, CannTrust, Canada, was involved in a case with the Canadian authorities for using unapproved cultivating grow rooms. As a result, STENOCARE immediately stopped the import and distribution of their products. Subsequently, one pharma-grade broad-spectrum cannabis product (THC/CBD, 1:2.5) was available, which contained active pharmaceutical Ingredients (API) of both THC and CBD. The API of THC and other organic compounds were extracted from dried cannabis flowers, Bedrocan (high THC, low CBD) by solvent extraction.

All products were manufactured under EU-GMP (European Union-Good Manufacturing Practice) standards, which ensured consistent cannabinoid concentrations in all the medical cannabis oils used in this study. All preparations were administered sublingually and kept in the mouth for 1-2 minutes before swallowing to ensure optimal oral mucosal absorption.

2.4. Study design and data collection

The present local study was a prospective, open-label, observational safety study conducted at one clinical center, The Danish Multiple Sclerosis Center, Copenhagen University Hospital. MS patients who initiated treatment with broad- or full-spectrum cannabis oils were observed during a titration period of four weeks, which included two visits: one baseline visit prior to treatment start (Visit 1) and one follow-up visit four weeks after (Visit 2). Each visit included neurological examination (Expanded Disability Status Scale – EDSS), ambulation (Timed 25-Foot Walk Test - T25FWT), routine blood tests including cannabinoids (THC, CBD, THC-CCOH, 11-OH-THC), assessment of dexterity (9-Hole Peg Test - 9-HPT) and processing speed (Symbol Digit Modalities Test - SDMT).

At Visit 1 patients were handed a diary to register their pain and/or spasticity intensity, AEs and dosing each day. The diary was returned at Visit 2, and the AEs and tolerability were assessed. All data were registered in the participants' electronic patient records. After the recruitment period all data were transferred to a secured database managing program, REDCap.

2.5. Routine blood tests

The routine blood tests included hemoglobin, white blood cell count, thrombocytes, albumin, calcium, calcium-ion, creatinine, estimated glomerular filtration rate, potassium, sodium, carbamide, alanine transaminase, basic phosphatase, lactate dehydrogenase, glucose, parathyroid hormone, thyroid stimulating hormone, C-reactive protein and vitamin D.

2.6. Selected cannabinoids and measurements

(−)-trans-Δ^9-tetrahydrocannabinol (THC) is the main psychoactive cannabinoid, produced by decarboxylation, when heated, of

tetrahydrocannabinolic acid (THCA), a cannabinoid found in fresh, undried cannabis. The primary metabolites of THC are the equipotent 11-hydroxy-Δ^9-tetrahydrocannabinol (THC-OH) and the inactive 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (THC-COOH), which are produced by hepatic hydroxylation. (Huestis, 2007) Cannabidiol (CBD) is a major constituent in the cannabis plant. In contrast to THC, CBD has no psychoactive effect, but has several other pharmacological properties such as antiepileptic, anti-inflammatory and anxiolytic effects. (Pisanti et al., 2017) If THCA is exposed to air or sunlight it is degraded to cannabinolic acid (CBNA), which by decarboxylation produces the cannabinoid cannabinol (CBN). CBN is mildly psychoactive and found in smaller quantities compared to the previously mentioned cannabinoids. (I.J. M., 2005)

To ensure stability of the cannabinoids, blood samples were immediately handled within 30 minutes, and blood plasma was stored at –80°C. THC, THC-OH, THC-COOH, CBD and CBN in plasma were quantified by an in-house developed method based on ultra-high-pressure liquid chromatography-mass spectrometry and utilizing corresponding deuterated internal standards for each compound. Plasma samples were prepared using a solid-phase extraction procedure. The analysis was performed on an ACQUITY UPLC I-Class system coupled to a Xevo TQ-S tandem mass spectrometer (both from Waters, Milford, MA), operated in positive-ion electrospray mode and using multiple-reaction monitoring. The measurement range was 0.2-50 ng/mL for all compounds except THC-COOH for which it was 0.5-50 ng/mL. The method was an extension and modified version of an earlier described method for THC. (Andersen et al., 2012)

Plasma cannabinoids were measured to determine concurrent cannabis use, e.g. use of illegally acquired products, at treatment start. This information made it possible to better interpret the results obtained after the titration period. The cannabinoid analyses, both at Visit 1 and Visit 2, were performed at the end of the study.

2.7. Outcomes

We assessed the primary outcomes for safety analysis by the frequency of AEs related to medical cannabis treatment. Patients ticked a list containing the following AEs: dry mouth, cognitive impairment, dizziness, nausea, drowsiness, headache, excessive thoughts, confusion, feeling subdued, depression, affected sensory impressions (hallucinations), felt persecuted (paranoia), heart palpations, increased sweating, anxiety and trouble at work. Participants had the option to add an AE if not on the list.

Every AE was categorized in severity as mild; moderate or severe. Furthermore, primary outcomes included changes in neurological examination (Expanded Disability Status Scale – EDSS), ambulation (Timed 25-Foot Walk Test - T25FWT), routine blood tests, plasma cannabinoids, dexterity (9-Hole Peg Test - 9-HPT) and processing speed (Symbol Digit Modalities Test - SDMT) between Visit 1 and Visit 2. In addition, patients were asked to report their perception of the manageability and usefulness of the titration guide and administration form, assessed by numeric rating scale (NRS) with an 11-point scale (0=no use, 10=very useful).

Secondary outcomes were treatment effectiveness, which was defined as changes in the intensity of pain, spasticity and sleep disturbances after 4 weeks of treatment assessed by NRS-11 (0 = no symptom, 10 = worst imaginable symptoms).

2.8. Titration protocol

Our dosing strategy was inspired by the practical considerations of dosing and administrations of medical cannabis addressed in a recent review article. (Maccallum and Russo, 2018) The strategy was based on the mantra ‘start low and go slow – and stay low’. Medical cannabis preparations containing considerable amounts (> 2 mg/mL) of THC (THC DROPS, 1:1 DROPS and THC/CBD 1:2.5) were dosed by the THC content. Initial dosage was 2.5 mg once a day, primarily at bedtime. The daily and longitudinal NRS-11 scores were used to evaluate the effect at the current dose. If no desired effect was obtained and the dose was well-tolerated, the dose was increased by 1.25 to 2.5 mg every third or fourth day. Alternatively, 2.5mg THC was given twice a day if required. The necessity for dose escalation was assessed by the patients. The dosage was maintained if desirable effects were obtained. Maximum daily dosage of THC was 22.5 mg with 7.5 mg per dose. In case of AEs, the dosage was reduced to the previous highest tolerated dosage. In regard of the CBD-predominant oil, CBD DROPS, initial dosage was 5.0 mg per day and increased by 5.0-10.0 mg every third/fourth day if tolerated and no desirable effects were achieved. Maximum dosage was 50 mg per day, which is a cautious approach considering the overall CBD safety profile examined in a recent review. (Larsen and Shahinas, 2020) In addition, patients had the opportunity to only take their cannabis medication when needed if they did not find a continuous daily use preferable.

Primarily THC and CBD combined preparations were recommended at treatment start due to the comparability to the regulatory approved and well-studied cannabis extract drug nabiximols (Sativex®). CBD-rich treatment was indicated if patients previously had experienced unacceptable side effects of THC products or were dependent on being able to drive a car.

2.9. Statistical analysis

Descriptive statistics including frequencies, percentages, means, medians and min-max intervals were used to summarize baseline characteristics and AEs. Comparison of paired measurements between Visit 1 and Visit 2 were performed by paired sample t-test or Wilcoxon Signed Rank Test depending on normality. The null hypothesis was that the means/medians of the two samples were equal. Normality was checked by histograms, Q-Q plots and the Shapiro-Wilk test. Statistical analysis was performed using Statistical Package for Social Science (SPSS) software (version 25, IBM)

3. Results

Twenty-eight patients with MS initiated treatment with medical cannabis oils during the recruitment period. Treatments were distributed as follows: THC:CBD 1:2.5 (n=13), THC:CBD 1:1 (n=10), THC-rich (n=1) and CBD-rich (n=4). Two patients discontinued treatment at day 10 and 14 in the titration period. One patient (treated with 1:1 DROPS) stopped the treatment due to unacceptable dizziness and drowsiness and one patient (treated with THC/CBD, 1:2.5) stopped because of lack of efficacy and excessive dreaming (see section 3.1. for further information). However, all data was obtained at Visit 2. Furthermore, two patients were not able to contribute with blood samples and tests at Visit 2 due to hospitalization and COVID-19 lockdown restrictions (**figure 1**). Treatment indications were neuropathic pain (n=22, 79%) and spasticity (n=21, 75%), and were primarily used as add-on therapy with simultaneously use of conventional analgesics and/or antispasmodics (**table 1**).

The mean THC dose was 4 mg/dose and CBD 7 mg/dose, and 19 out of 26 (73%) only used one dose daily, primarily in the evening. Otherwise, the treatment was taken 3 times daily.

3.1. Adverse events (AEs)

The most reported AEs were dry mouth, drowsiness, dizziness and nausea, and were associated with medical cannabis oils containing THC levels > 2 mg/mL (**table 2**). These AEs also occurred at relative low doses, e.g. 2.5 mg THC. Two patients reported AEs with severe intensity. This included drowsiness and excessive dreaming with horrible nightmares, respectively, which made the patients stop the treatment during the titration period. No psychotic symptoms, e.g. paranoia, delusions or

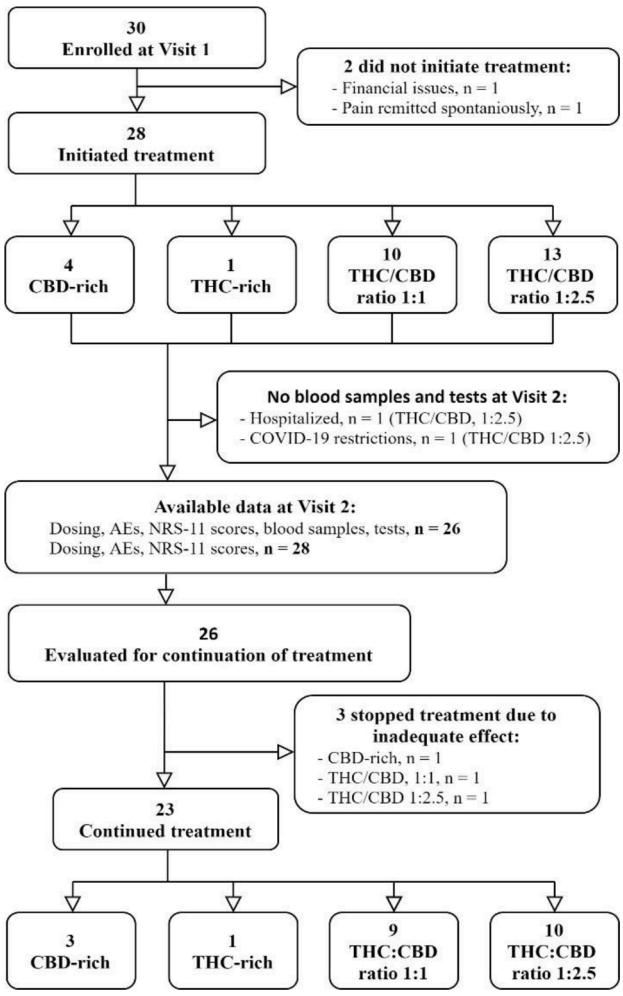

Figure 1. Study flowchart

hallucinations were reported. Euphoria was reported two times and at relatively higher THC doses, 6.3 and 22.5 mg, respectively. When the dosage was reduced the euphoria resolved. The AEs were primarily reported mild in intensity, appeared 30-60 minutes after administration and resolved spontaneously after 1-2 hours. Three serious adverse events (SAE) were reported, which required hospitalization, but were not associated with the treatment. One patient was hospitalized due to abdominal cramps and watery diarrhea caused by a Giardia infection, one patient because of jaw-bone infection and the third patient because of high fewer and respiratory distress caused by COVID-19. One patient treated with CBD DROPS reported dizziness, nausea, confusion and headache, but the association with the treatment was not clear, because the AEs only happened once during the titration period, approximately 12 hours after administration and lasted for 3-4 hours. Otherwise, drowsiness was the only reported AE when treated with CBD-rich products. No difference was observed in the frequency of reported AEs when comparing cannabis-naïve individuals with previous cannabis users.

3.2. Efficacy

Statistically significant decreases in pain, spasticity and sleep disturbance intensity were reported for patients treated with THC-containing (10-25 mg/mL) products (table 3). Likewise, decreases in pain, spasticity and sleep disturbances among patients treated with the CBD predominant product were observed. However, the results were not statistically significant, presumably because of the small sample size

Table 1
Baseline characteristics

	Total *n=28*
Age, mean (min-max)	50 (27-74)
Sex, n (%)	
Men	7 (25)
Women	21 (75)
Clinical type of MS, n (%)	
Relapse-remitting MS (RRMS)	15 (53)
Secondary progressive MS (SPMS)	8 (29)
Primary progressive MS (PPMS)	5 (18)
Duration of diagnosis, years, median (min-max)	11 (1-28)
Expanded Disability Status Scale (EDSS), median (min-max)	4.5 (2-9)
Treatment indications, n (%)	
Chronic neuropathic pain	22 (79)
Spasticity	21 (75)
Concomitant analgesic treatment, n (%)	
Paracetamol	19 (86)
Nonsteroidal anti-inflammatory drug (NSAID)	8 (36)
Tricyclic antidepressant (TCA)	3 (14)
Anticonvulsants (gabapentin, pregabalin)	4 (18)
Serotonin-norepinephrine reuptake inhibitors (SNRI)	2 (9.1)
Weak opioids	2 (9.1)
Strong opioids	1 (4.5)
Concomitant antispasmodic treatment, n (%)	
Baclofen, oral	5 (24)
Tizanidine	3 (14)
Baclofen, intrathecal	1 (4.7)
Botulinum toxin injections	2 (9.5)
Previous cannabis use, n (%)	23 (82)
On prescription	
Dronabinol (Marinol)	2 (8.7)
Nabiximols (Sativex)	4 (17)
Acquired illegally	
Inhalation (e.g. marijuana, hashish, pot, skunk)	2 (8.7)
Oral/sublingual (content unknown to patient)	17 (74)

(n=4).

3.3. Routine blood tests, clinical tests and levels of plasma cannabinoids

No impairment on disability, ambulation, dexterity or processing speed was observed. However, statistically significant improvement was observed in T25FW and 9HPT performance when results from Visit 1 and Visit 2 were compared. No differences were observed in the EDSS or SDMT scores (table 4). No clinically significant changes or statistically significant differences in any of the routine blood tests were observed. At Visit 1 seven patients had detectable cannabinoids. Of those, three had traceable THC + THC-COOH, two CBD and two THCCOOH (data not shown). The three patients with detectable THC changed from illegal cannabis use to medical cannabis oils at treatment start. The other four patients had stopped illegal cannabis use 1-2 weeks prior to treatment start. CBN was not detected in any of the blood samples. At VISIT 2, cannabinoids were analyzed in 26 patients, see table 5 for description of used cannabis product, THC and CBD dosage (mg/dose), time between last dose and blood sample (hours), and cannabinoid levels (mg/kg). Time of blood sample from last dose was primarily 10-12 hours (n=19) or 2-3 hours (n=4). All blood samples were drawn before noon. The time from blood sample from last dose therefore depended on whether the patients were administered a morning dose or only an evening dose. Three patients had blood drawn >24 hours after last dose, which included the two patients who discontinued treatment due to lack of efficacy and unacceptable dizziness. These three patients were not included in the assessment of the association between THC dose and plasma THC concentration (figure 2). Furthermore, we observed no deviant THC or THC-COOH concentration peaks and the plasma cannabinoid profile matched the prescribed preparations.

Table 2
Frequencies of reported adverse effects (AE). AEs noted in brackets: no clear association with medical cannabis. The single-dose range indicates at which doses the AEs occurred.

Cannabis preparationand adverse effect (AE)	N (%)	Intensity of AE			Single-dose range when reporting AE, mg	
		mild	moderate	severe	THC	CBD
THC and CBD (1:1 DROPS), n=10						
Dry mouth	6 (60)	6			2.5-7.5	2.5-7.5
Dizziness	4 (40)	3	1		3.8-7.5	3.8-7.5
Concentration problems	3 (30)	2	1		3.8-7.5	3.8-7.5
Drowsiness	2 (20)	1	1		7.5	7.5
Headache	2 (20)	2			6.3-7.5	6.3-7.5
Confusion	1 (10)	1			7.5	7.5
Heart palpations	1 (10)	1			6.3	6.3
Increased sweating	1 (10)	1			6.3	6.3
Trouble at work	1 (10)	1			6.3	6.3
Euphoria	1 (10)	1			6.3	6.3
Increased appetite	1 (10)	1			10	10
THC and CBD (1:2.5), n=13						
Nausea	5 (38)	4	1		2.5-4.3	6.2-11
Heart palpations	4 (31)	3	1		2.5-3.1	6.3-7.8
Dru mouth	3 (23)	3			2.5-4.3	6.2-11
Dizziness	3 (23)	1	2		2.5-4.3	6.2-11
Drowsiness	3 (23)	2		1	3.1	7.8
Increased sweating	2 (15)	1	1		3.1	7.8
Excessive dreaming	1 (7.7)			1	3.1	7.8
Trouble at work	1 (7.7)		1		3.1	7.8
Concentration problems	1 (7.7)	1			4.3	11
Headache	1 (7.7)	1			1.6	4.0
Sadness	1 (7.7)	1			3.1	7.8
THC rich (THC DROPS), n=1						
Dizziness	1 (100)	1			22.5	1
Euphoria	1 (100)	1			22.5	1
CBD rich (CBD DROPS), n=4						
Drowsiness	2 (50)	1	1		<1–1	3.75-15
(Dizziness)	1 (25)	1			<1	3.75
(Nausea)	1 (25)	1			<1	3.75
(Confusion)	1 (25)	1			<1	7.5
(Headache)	1 (25)	1			<1	3.75

Table 3
Efficacy of medical cannabis oils on neuropathic pain, spasticity and sleep disturbances.

	Intensity – NRS¤, median (min/max)		Median difference (min/max)	*p*-value*
	Visit 1	Visit 2		
THC 10-25 mg/ml, n=24				
Neuropathic pain, n=19	7.0 (2.0/9.0)	3.0 (1.0/8.0)	- 3.0 (-7.0/0.0)	**0.01**
Spasticity, n=18	6.0 (1.0/10)	2.5 (0.0/7.0)	- 2.5 (-9.0/0.0)	**0.01**
Sleep disturbances, n=24	7.0 (0.0/9.0)	3.0 (0.0/10)	- 3.0 (-7.0/2.0)	**<0.01**
CBD-rich (THC ≤ 2 mg/ml), n=4				
Neuropathic pain, n=3	7.0 (7.0/8.0)	5.0 (4.0/7.0)	- 3.0 (-7.0/-1.0)	0.10
Spasticity, n=3	6.0 (4.0/8.0)	2.0 (2.0/2.0)	- 4.0 (-6.0/-3.0)	0.11
Sleep disturbances, n=4	8.0 (3.0-10)	0.0 (0.0-1.0)	- 7.0 (-10/-3.0)	0.07

¤NRS: Numeric rating scale, 0 = no symptoms, 10 = worst imaginable symptoms
*Wilcoxon Signed Ranks Test. Bold values indicate statistically significance ($p < 0.05$)

3.4. Manageability and usefulness of the titration guide

The median NRS scores (0 = no use to 10 = very useful) and interquartile range (25% - 75%) for manageability and usefulness of the titration guide were 9 (7.25 – 10.0) and 9 (8.0 – 10.0), respectively.

4. Discussion

We found that treatment with medical cannabis oils was safe and well tolerated, and resulted in a reduction in perceived pain intensity, spasticity and sleep disturbances in patients with MS. This matches previous findings: however, these studies primarily included formulations of cannabis medicine as oromucosal spray, dried flowers or oral capsules (Nielsen et al., 2018) and did not address the exact dose when the AEs occurred. Importantly, we observed that AEs also occurred at low doses, e.g. 2.5 mg THC; therefore, it is important to initiate treatment with low doses.

We did not see any impairment in disability, ambulation, dexterity or processing speed. In fact, we found a statistically significant improvement in T25FW and 9HPT; however, due to the small median differences between the scores at Visit 1 and Visit 2 (Table 4) we do not consider this a clinically significant improvement.

Another important finding is that treatment with medical cannabis oils reduced the intensity of pain, spasticity and sleep disturbances. The intensity of spasticity reduced with a median difference of -2.5 on the NRS-11 scale, which is consistent with the results from a study by Wade et al. (Wade et al., 2004) In the study MS patients were treated with an oromucosal cannabis extract (Sativex®). They found a mean reduction on the visual analog scale (VAS) of 26.5 to 31.2 for spasms/spasticity. In our study pain intensity was reduced by 3.0 (NRS-11, median

Table 4
Clinical tests and disability status.

	Median (min/max)		Median difference (min/max)	*p*-value*
	Visit 1	Visit 2		
9-HPT, mean, seconds, n=22				
Dominant hand	23.0 (16/58)	22.1 (16/49)	- 1.7 (-8.9/2.8)	**<0.01**
Non-dominant hand	23.3 (18/85)	22.5 (18/63)	- 0.8 (-22/4.5)	0.11
T25FW, mean, seconds, n=23	5.5 (3.4/36)	5.0 (2.8/36)	- 0.3 (-2.4/0.8)	**<0.01**
SDMT, median, n=22	51 (34/84)	50.5 (28/82)	2.0 (-13/9.0)	0.12
EDSS, median, n=26	4.5 (2.0/9.0)	4.3 (1.0/9.0)	0.0 (-1.0/1.0)	0.06

*Wilcoxon signed rank test. Comparison between Visit 1 and Visit 2. Bold values indicate statistically significance ($p < 0.05$). Abbreviations: 9-HPT, nine-hole peg test; T25FWT, timed 25-foot walk test; SDMT, single digit modalities test; EDSS, expanded disability status scale.

difference), which is a higher reduction compared to the study by Wade et al. that found a mean NRS-11 pain reduction of 1.1 in the active group. Additionally, they did not find a statistically significant difference between the treatment and the placebo group. Overall, previous studies have shown inconsistent results on the effect of Sativex® on pain in MS patients. (Nielsen et al., 2018) A systematic review of clinical and preclinical trials investigating the effect of THC and CBD on sleep disorders concluded that the evidence to support treatment with THC and CBD was insufficient. (Suraev et al., 2020) In our study, we observed a statistically significant improvement in sleep disturbances. However, we were not able to distinguish whether the effect on sleep disturbances was directly improved by the treatment, or as a secondary effect due to the improvement in pain and spasticity in the evening and nighttime.

The strengths of this study are the prospective design, and because of the clinically heterogeneous nature the cohort reflects a 'real-world' MS population with diverse clinical manifestations. In addition, we measured plasma cannabinoids to ensure that patients did not use other cannabis products during the treatment period. In this study, patients were treated with EU-GMP-certified medical cannabis oils with concentration data, which guarantied quantification of THC and CBD in the end-products, and thereby ensured dosage repeatability. In previous safety studies, on medical cannabis oils, the end-product concentrations of THC and CBD were not always quantified and/or the manufacturing standards were not described. (Sagy et al., 2019, Palmieri et al., 2019, Shelef et al., 2016). An Italian study found a remarkable 20-fold variation in cannabinoid concentrations among 201 galenic oil preparations from 10 different pharmacies. (Carcieri et al., 2018) This emphasizes the importance of ensuring high quality manufacturing standards to provide reliable concentration data, and thereby avoid potency variability. Furthermore, we observed no deviant THC or THC-COOH concentration peaks (**figure 2**), and the plasma cannabinoid profile matched the prescribed preparations. This suggests that patients did not use other cannabis products, e.g. smoked marijuana or other high potency cannabis products during the titration period. To optimize the comparison between visits the tests (T25FW, 9HPT and SDMT), neurological examination (EDSS) and treatment evaluations, were performed by the same physician.

Limitations include the small clinically and demographically heterogeneous cohort, and the uncontrolled, unblinded design. Both the patient and the treating physician were aware of the treatment received. The placebo effect is a strong modulating mechanism in clinical trials with pain intensity as an outcome due to expectancy-induced analgesia. On the other hand, a strong placebo response can lead to an underestimation of intervention effect. (Lund et al., 2014)

Table 5
Medical cannabis treatment and cannabinoid plasma levels, listed by subjects, n=26. THC and CBD doses represent the last dose that was taken prior to Visit 2.

THC, mg/dose	CBD, mg/dose	Cannabis preparation	Time of blood sample from last dose (h)	Visit 2 Cannabinoid plasma levels, ng/mL			
				THC	CBD	THC-COOH	THC-OH
7.5	7.5	1:1 DROPS	2-3	3.6	4.0	19.3	3.4
7.5	7.5	1:1 DROPS	2-3	2.1	7.9	60.2	2.3
6.0	15.0	THC/CBD (1:2.5)	2-3	1.1	3.7	41.6	2.3
4.3	10.8	THC/CBD (1:2.5)	2-3	2.1	11.9	9.3	1.4
12.5	1.0	THC DROPS	10-12	1.1	0.2	17.0	ND
7.5	7.5	1:1 DROPS	10-12	0.3	0.6	3.1	ND
6.3	6.3	1:1 DROPS	10-12	0.4	2.1	6.8	0.6
5.0	5.0	1:1 DROPS	10-12	0.2	1.1	7.2	ND
4.3	10.8	THC/CBD (1:2.5)	10-12	0.2	1.0	5.7	ND
3.8	3.8	1:1 DROPS	10-12	ND	ND	7.8	ND
3.8	3.8	1:1 DROPS	10-12	ND	0.3	10.3	ND
3.8	3.8	1:1 DROPS	10-12	0.2	0.7	2.7	0.2
3.7	9.8	THC/CBD (1:2.5)	10-12	ND	0.7	6.2	0.3
3.1	7.8	THC/CBD (1:2.5)	10-12	ND	0.3	2.4	ND
3.1	7.8	THC/CBD (1:2.5)	10-12	ND	0.3	3.7	ND
2.5	2.5	1:1 DROPS	10-12	0.4	0.5	7.6	0.4
2.5	6.3	THC/CBD (1:2.5)	10-12	ND	0.5	13.9	0.4
2.5	6.3	THC/CBD (1:2.5)	10-12	ND	0.5	22.7	0.4
1.6	4.0	THC/CBD (1:2.5)	10-12	ND	0.4	1.8	ND
1.0	15.0	CBD DROPS	10-12	ND	1.1	4.2	ND
1.0	7.5	CBD DROPS	10-12	ND	0.7	2.8	ND
1.0	10.0	CBD DROPS	10-12	ND	0.3	ND	ND
0.0	3.8	CBD DROPS	10-12	ND	0.4	ND	ND
3.5	8.8	THC/CBD (1:2.5)	24-36	ND	ND	1.3	ND
2.5	6.3	THC/CBD (1:2.5)	14 days*	ND	ND	ND	ND
3.8	3.8	1:1 DROPS	18 days*	ND	ND	ND	ND

*Patients who stopped treatment during the titration period.
ND: not detected.

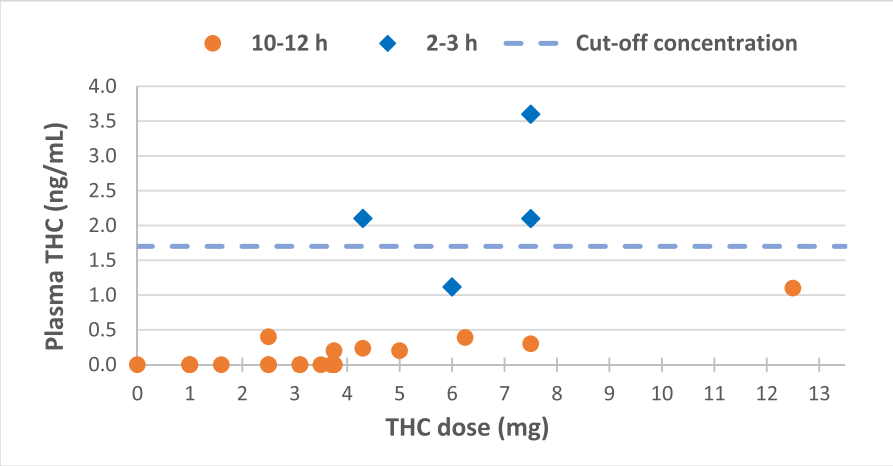

Figure 2. THC dose and plasma concentrations at Visit 2, n = 23. Hours between last dose and blood sample (h). The cut-off concentration indicates the THC limit in accordance to the Danish legislation when driving.

Driving under the influence of cannabis in Denmark is illegal without a prescription. The cut-off concentration of THC is 0.001 mg/kg whole blood. In our study cannabinoids were measured in plasma. The whole blood/plasma ratio of THC is approximately 0.6 (Karschner et al., 2012) and the plasma density is 1.025 g/mL, thus the cut-off concentration of 0.001 mg/kg in whole blood corresponds to a cut-off concentration of 1.7 ng/mL in plasma. An additional finding in this study was that every patient with blood samples drawn 10-12 hours after last dose had plasma THC concentrations lower than the cut-off concentration, even at a dose of 12.5 mg THC. These results are consistent with the results from a phase I study, which assessed the pharmacokinetics of THC/CBD oromucosal spray (Sativex®) at single and multiple doses. (Stott et al., 2013) Furthermore, we did not find any impairment in dexterity (9-HPT), processing speed (SDMT) or ambulation (T25FWT) when treated with medical cannabis, which would indicate impaired driving capabilities. The pharmacokinetic data on the association between THC dose and plasma THC concentration were not investigated at the exact same time for each patient, and patients were not recommended to take the medicine with or after food intake, which is why the conclusion on safety in relation to driving could not be assessed. Because of limited pharmacokinetic data on medical cannabis oils administered sublingually, (Poyatos et al., 2020) and its potential impairment of key functions needed for driving, (Fischer et al., 2017) patients were at treatment start recommended not to drive during the treatment.

A recent study reviewed the evidence relating Sativex® and its impact on driving performance. (Celius and Vila, 2018) The authors concluded that Sativex® did not impair driving performances. However, there still is a strong need, due to the present relatively small sample studies, for larger clinical studies to clarify the pharmacokinetic parameters of sublingually administered cannabis products to optimize guidelines for driving.

4.1. Recommended dose titration

Based on the study results, despite its limitations, the following dose titration is recommended when initiating treatment with sublingual medical cannabis oils: Start with a low dose of 1.25 mg THC. If tolerated the dose can be increased by 1.25 mg every third day until the desired effect is achieved. A maximum daily dosage of 20-25 mg THC and a maximum of 7.5 mg per dose is recommended. This recommendation is a more cautious approach than the aforementioned recommendations. (Maccallum and Russo, 2018) A possible reason could be the route of administration. Sublingual administration has a faster onset of action, approximately 15-45 minutes, compared to oral administration. Because of the small sample of four patients being treated with CBD rich oils, it is not possible to draw any conclusions regarding dosage recommendations.

In conclusion, this study suggests that treatment with sublingual medical cannabis oils are safe and efficient, but also emphasize the importance of initiating treatment with low doses and slow titration. Placebo-controlled, double-blind studies of the efficacy and safety of cannabis oils are warranted.

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Ethics statement: The study was approved by the Danish Data Protection Agency, Copenhagen, Denmark and the Danish Health and Medicines Authority, Copenhagen, Denmark (Journal-nr.:H-18002478). All patients signed informed consent.

Funding

We thank the Torben and Alice Frimodts foundation and Helsefonden for their financial support, e.g. covering the cost of the cannabinoid analyses.

Declaration of Competing Interest

A.B Oturai: has served on scientific advisory boards for Biogen Idec, Novartis and Sanofi Genzyme; has received research support from

Novartis and Biogen Idec; has received speaker honoraria from Biogen Idec, Novartis and TEVA; and has received support for congress participation from, Merck, TEVA, Biogen, Roche, Novartis and Sanofi Genzyme. P.S. Sørensen: has received personal compensation for serving on scientific advisory boards, steering committees, independent data monitoring committees or have received speaker honoraria for Biogen, Merck, Novartis, TEVA. F. Sellebjerg: has served on scientific advisory boards, been on the steering committees of clinical trials, served as a consultant, received support for congress participation, received speaker honoraria, or received research support for his laboratory from Biogen, Merck, Novartis, Roche, and Sanofi Genzyme; and is section editor on Multiple Sclerosis and Related Disorders. S. Gustavsen: has received support for congress participation from Merck and has worked at a private pain clinic, Clinic Horsted, with expertise in cannabis, to gain knowledge on how to initiate medical cannabis treatment and dosing regimes.. B.S. Rasmussen, R. Thomsen, K. Linnet and H.B. Søndergaard: none.

Acknowledgements

We would like to thank Annette Larsen and Joy Melchert at the Danish Multiple Sclerosis Center, Copenhagen University Hospital, Rigshospitalet for organizing the study visits, and the personnel at the Department of Clinical Biochemistry Copenhagen University Hospital, Rigshospitalet for preparing and sending blood samples for cannabinoid analysis to the Department of Forensic Medicine, Section of Forensic Chemistry, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.

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