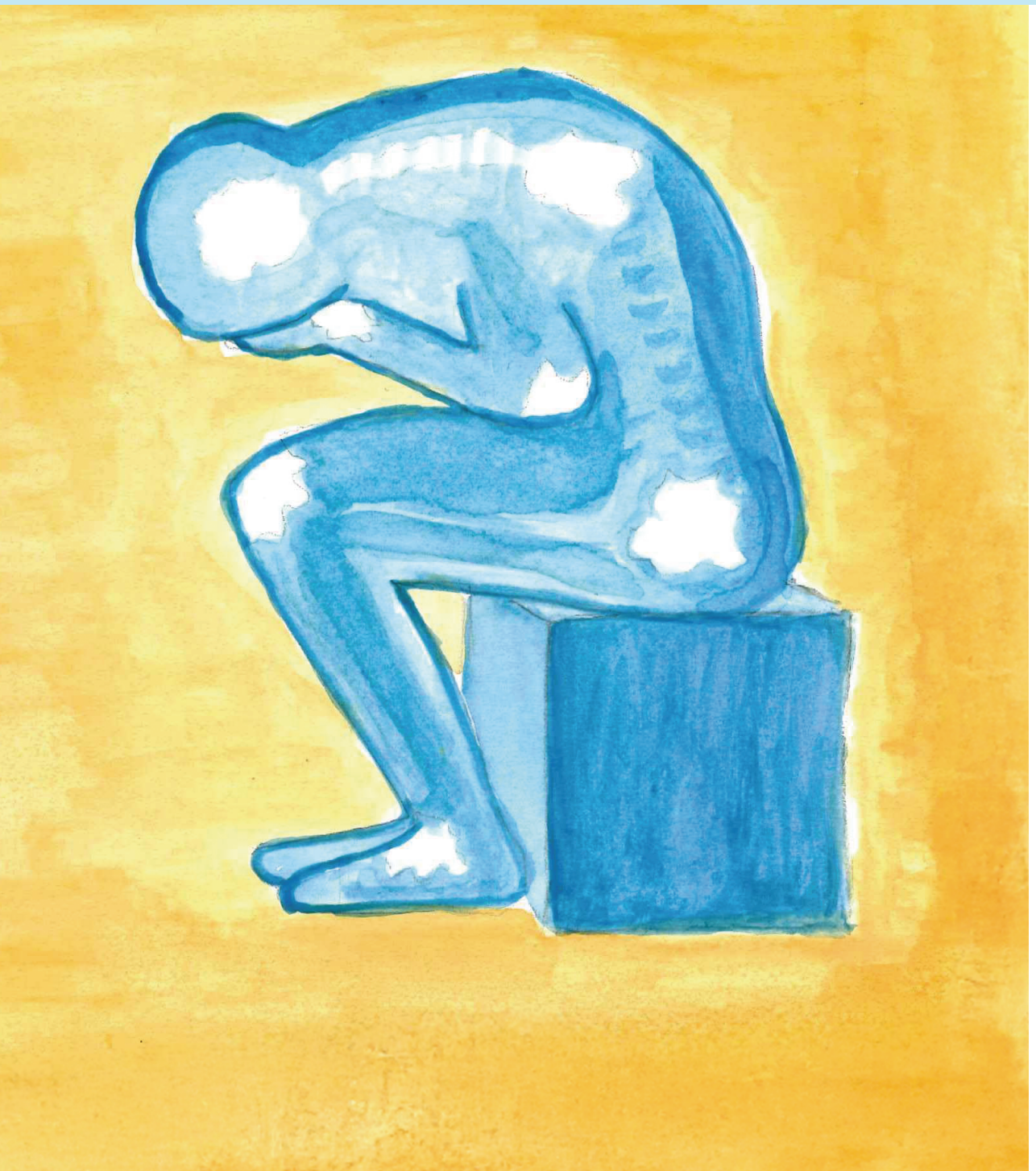
Opioid and cannabis utility: effects and side-effects in the of chronic pain

Dam, C.J. van



Chapter 7

Effects and Side Effects in Cannabis, Oxycodone or Cannabis/Oxycodone Combination Treatment in Fibromyalgia Pain: a Randomized Clinical Self-Titration Trial with Focus on Adverse Events

Cornelis Jan van Dam, Cornelis Kramers, Arnt Schellekens, Marcel Bouvy, Eviline van Dorp, Mikael A Kowal, Erik Olofsen, Albert Dahan, Marieke Niesters, Monique van Velzen

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7.1 ABSTRACT

Objectives: We determine whether adding cannabis to oxycodone for chronic noncancer pain management would reduce treatment-related adverse effects (AEs) while maintaining analgesia.

Methods: In this open-label study, fibromyalgia patients, aged ≥18 years, were randomized to receive 5-mg oxycodone tablets (max. 4-times/day), 150 mg inhaled cannabis containing 6.3% Δ^9-tetrahydro-cannabinol and 8% cannabidiol (max. 5 inhalation sessions/day) or their combination, for 6-weeks. The main endpoint was treatment-related adverse events reported using a 10-point composite adverse event score (cAE); additionally, we collected daily reported pain relief and daily tablet and cannabis consumption.

Results: Twenty-three patients were treated with oxycodone, 29 with cannabis and 29 with the oxycodone/cannabis combination. Three patients treated with just oxycodone (13%) and 18 patients treated with cannabis (31%, 9 in either groups) dropped out of the trial within 2-3 weeks because of severity of AEs. There were no differences in treatment-related cAEs among the three groups that completed the study (p=0.70). The analgesic responder rate was ≥1 pain point reduction in 50% and ≥2 points reduction in 20% of patients; 50% of patients were without treatment benefit. The treatment combination reduced oxycodone tablet consumption by 35% (p=0.02) but not the number of cannabis inhalation sessions.

Conclusions: Cannabis combined with oxycodone had no advantage over either treatment alone, apart from the reduced opioid tablets intake, albeit the overall drug load was highest in the combination group. Moreover, cannabis was poorly tolerated and led to treatment discontinuation in a third of participants treated with cannabis.

7.2 INTRODUCTION

Opioids are widely prescribed for the management of chronic noncancer pain, despite the awareness that opioids offer only temporary pain relief, is associated with an increase in dose due to tolerance development, come with a multitude of side effects (including dizziness, sedation, nausea/vomiting, constipation, hyperalgesia, addiction, respiratory depression) and pose challenges when attempting to discontinue due to the development of dependence and withdrawal symptoms.[1,2] One possibility to reduce or even eliminate the opioid consumption is to manage pain according to a multimodal approach including pharmaceutical-grade cannabis.[3] We previously showed that a single dose of inhaled pharmaceutical-grade cannabis variety Bediol®, that contains Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD), reduces experimental pain and spontaneous pain in patients with pain due to fibromyalgia syndrome for short periods of time.[4] Prior research indicates that using several cannabis varieties (all non-pharmaceutical-grade varieties) for the management of chronic pain can lead to a reduction of opioid consumption, albeit not in all patients.[5-8] However, a systematic review from 2020 that included more than 7,000 noncancer patients with chronic pain, found that while opioid dosage decreased in the majority of patients when medicinal cannabis was combined with opioids, all included studies had a high risk of bias and causal inference was often not possible.[9] At present, there is no consensus on whether combining opioids with cannabis yields a positive health benefit, *i.e.* an improved balance between pain relief and AEs, and additionally the optimal cannabis doses for reduction of opioid consumption remain unknown.[9]

In our current study, we hypothesized that adding the cannabis strain Bediol® to oxycodone treatment has advantages over just oxycodone or just cannabis in the treatment of patients with fibromyalgia experiencing modest to severe pain. The study was designed so that patients could self-titrate their oxycodone and cannabis doses (with strict limitations) over a 6-week period.[10] The primary objective of the study was to assess and compare drug-related side effects in fibromyalgia patients treated with either cannabis combined with oxycodone versus just oxycodone or cannabis. At this point we would like to highlight that opioids and cannabinoids are not recommended for the treatment of fibromyalgia, but that some patients do receive these treatments and side effect profiles need to be studied, and strategies for weaning off these drugs deserve to be put in place. See also the EULAR, NICE and Health Council of the Netherlands (Gezondheidsraad) recommendations for treatment of chronic pain in fibromyalgia.[11-13]

7.3 METHODS

7.3.1 Ethics and registration

The Leiden University Medical Center medical ethical review board approved the protocol, which was subsequently published.[10] All subjects gave written informed consent prior to enrollment in the study. The study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines and was performed from December 2019 to November 2022. The trial was registered at the WHO International Clinical Trials Registry Platform (trialsearch.who.int) on July 26, 2019, identifier NL7902.

7.3.2 Patients

Patients, aged 18 years or older of either sex with a diagnosis of fibromyalgia, were recruited. Inclusion criteria were: chronic (>3 months) pain with a pain score ≥5 (on a scale from 0 = no pain to 10 = most severe pain imaginable) for most of the day and diagnosed with fibromyalgia according to the 2016 American College of Rheumatology criteria.[4,14,15] These criteria include: a widespread pain index ≥7 (on a scale from 0-19), and a symptom severity score ≥5 (on a scale from 0-12) or a widespread pain index of 3-6 and a symptom severity score ≥9. The widespread pain index defines the number of body areas in which a patient experienced pain during the last week; the symptom severity score indicates the level of other core symptoms of fibromyalgia such as fatigue, non-refreshing sleep and cognitive symptoms.[14]

Exclusion criteria were[10]: a medical disease or comedication that could alter the pharmacokinetics of cannabis or oxycodone, allergy to study medication, prior use of cannabis, inability to taper down on previous pain medication (including strong opioids or tramadol) in the 2 weeks prior to dosing, history of illicit drug abuse or alcohol abuse, a history of psychosis, pregnancy and/or lactation, the presence of pain syndromes other than fibromyalgia. The use of any other opioid other than oxycodone provided by the investigators during the trial was not allowed. In case the patients used opioids before study participation, the drug was tapered down to zero opioid use in the 2-weeks prior to dosing. The use of paracetamol, gabapentin or pregabalin was allowed provided the medication was consumed for at least 6-weeks at a fixed dose. The presence of autonomic complaints such as diarrhea or obstipation or dizziness were not a reason for exclusion, as these are symptoms consistent with the fibromyalgia syndrome.[14,15]

7.3.3 Study design and treatment

The study had an open-label, randomized design. Patients with chronic pain from fibromyalgia were randomized 1:1:1 to self-titrate 5 mg oral oxycodone sustained release tablets (Mundipharma Pharmaceuticals BV, the Netherlands), 150 mg inhaled cannabis (Bediol®, Bedrocan International BV, the Netherlands) that contains 6.3% THC (9.5 mg), 8% CBD (12 mg) and has a specific terpene profile (including myrcene, α_2-pinene, terpinolene, β-caryophyllene, cis-ocimene, α-terpineol, all > 0.5 mg/g; see https://bedrocan.com/wp-content/uploads/bediol-terpene-profile.pdf), or their combination for 6-weeks with 6 weeks follow-up. Patients that were treated with cannabis received capsules that contained 150 mg cannabis of the Bediol® variety. The capsules could be placed in a hand-held vaporizer, the Mighty Medic (Storz & Bickel GmbH & Co, Germany) that was made available to the patients for home use. The vaporizer heats the plant material to allow conversion of the THC and CBD acids into active THC and CBD for inhalation. The patients inhaled cooled cannabis vapor from the vaporizer in sessions lasting 3-5 min. The study was performed in a single center (LUMC) where the patients received their medication; all patients were treated at home. The cannabis formulation and dose used in this study was based on our earlier study comparing the effect of three cannabis varieties, and observed that the Bediol® variety was most effective in reducing fibromyalgia pain.[4]

Randomization was performed in the Castor data capture system (www.castoredc.com) by the study team on day prior to dosing. Patients randomized to oxycodone treatment could use up to two (5 mg) oxycodone tablets per day in week 1 of treatment, and subsequently in weeks 2-6, up to four oxycodone tablets per day. Patients randomized to cannabis treatment, were instructed by the study team to use up to three (150 mg) cannabis capsules per day in week 1 of treatment, and subsequently in weeks 2-6, up to five capsules. Patients randomized to the combination of cannabis and oxycodone, were allowed to use up to two oxycodone tablets and up to three cannabis capsules per day in week 1 of treatment, and up to four oxycodone tablets and up to five cannabis capsules per day during treatment weeks 2-6. Medication was prepared by the pharmacy and provided to the patients through the study team.

7.3.4 Measurements

Endpoints

The main study outcome was the number of daily AEs scored during the course of treatment. To that end, a practical cAE score was used that included the following 10 symptoms: dizziness (when getting up), sleepiness, insomnia, headache, nausea,

vomiting, constipation, drug high, hallucinations, and paranoia. The included symptoms encompassed opioid and cannabis AEs. The subjects were requested to score these symptoms at the end of each day of treatment as they had occurred during that day. Scoring of a symptom resulted in 1-point (minimum score per day = 0, *i.e.,* there were no symptoms; max. score per day = 10, *i.e.,* all symptoms occurred; maximum score for the complete 42-day treatment period = 420). The comparisons were cAEs observed in the oxycodone/cannabis arm *versus* either treatment alone. Severity of AEs were not considered in the cAEs but were considered when patients decided to drop out of the study. In such cases the occurrence of AEs was assessed quantitively (moderate, severe, unacceptable).

Pain experienced on average over the last 24 h and related to the fibromyalgia pain was daily scored by the patient, and was the secondary endpoint of the study. The pain was scored on a 11-point numerical rating scale (NRS) from 0 (= no pain) to 10 (= most pain imaginable). We used numerical rating score rather than the more complex scoring used during screening, as we felt that a simpler score was more reliable.

Finally, the number of oxycodone tablets and the number of cannabis inhalation sessions was an exploratory endpoint.

7.3.5 Data analysis

Sample size

Sample size calculations were based on the primary outcome, the cAE score with AEs occurring from drug treatment. To that end, a power analysis was performed using Monte Carlo simulations. In brief, the count of side effects data was assumed to be binomially distributed. One-hundred simulated data sets were fitted to a mixed effects model (using glmer in R), and the number of times the p-values for the test for significance of the interaction term (time*treatment) were below alpha = 0.05 were counted. In the opioid-only group, the counts were assumed to be around 5 over time; in the group cannabis/oxycodone, the counts were assumed to decrease by 20% over time to 4. Inter-occasion plus interindividual variability of the time*treatment effect was assumed to have an SD of 0.3 at the end of the 6 weeks. For a power of 80%, 22 subjects in each arm were needed, for a power of 90% 29 subjects were needed. The 20% decrease in counts was determined by consensus in our pain groups and additionally based on experience in earlier studies in which a 20% decrease in adverse effects was deemed a significant improvement of the quality of life by the patients.[4,10]

Statistical analysis

We performed intention-to-treat and per protocol analyses on cAE data and pain scores, and a per protocol analysis on tablets used. The cAE and pain data were compared among treatments using linear mixed models in the statistical package NONMEM version 7.5.1 (ICON Development Solution, USA); p-values were computed using the χ^2-test based on differences of minus two log-likelihood values. Missing data were imputated using linear interpolation. cAE and pain scores were analyzed from days 14-42 of treatment. We left weeks 1 and 2 out of the cAE and pain relief analyses as these were considered the titration phase towards a steady-state treatment phase, they were considered when reporting dropouts. Dropouts were analyzed by Kaplan-Meier analysis and log-rank (Mantel-Cox) test in GraphPad Prism, version 10.2.3 for Mac OS (GraphPad Software, Boston, MA, USA). Reported medication use was compared between groups by unpaired non-parametric t-tests in GraphPad Prim 10. P-values of < 0.05 were considered significant. Subjects that dropped out of the study were replaced to ensure that 20 subjects completed the study in each treatment arm; all patients that started the study were included in the intention-to-treat analysis.[10]

7.4 RESULTS

A total of 128 patients were screened for eligibility (Fig. 1). Patient characteristics are given in Table 1 showing little differences among groups at baseline. The majority of included patients was female with just 2 men included in the study. Drop outs did not differ in demographic or disease characteristics compared to subjects that successfully completed the 6-week treatment period. Prior to their inclusion in the study, 20% of randomized patients used no analgesic medication, 34% of patients used one analgesic and 46% used at least 2 analgesics (median 2 with range 2 to 4). There was no difference among treatment groups in analgesic use with most frequent drugs used: paracetamol in 42% of patients, non-steroidal anti-inflammatory drugs (42%), opioids (tramadol, codeine, oxycodone: 22%), amitriptyline (16%), pregabalin (12%), and duloxetine (6%).

Table 1. Patients characteristics at baseline

	Oxycodone	Cannabis + Oxycodone	Cannabis
Total number of patients	23	29	29
Women	23	28	28
Age (year)	46.9 ± 16.0	37.1 ± 13.4	44.2 ± 14.1
Weight (kg)	77.5 ± 17.1	76.0 ± 13.3	70.8 ± 13.3
Height (cm)	168 ± 6	169 ± 8	167 ± 7
BMI (kg/m^2)	27.1 ± 5.7	27.2 ± 4.3	27.1 ± 5.2
Fibromyalgia symptoms			
Widespread pain index (0-19)	14.3 ± 3.1	14.5 ± 2.9	15.1 ± 3.1
Symptom severity (0-12)	8.6 ± 1.7	8.3 ± 1.7	8.7 ± 2.1
Tender Points (0-18)	13.8 ± 3.9	13.6 ± 3.1	14.3 ± 2.6
Pain characteristics			
Average score	6.3 ± 1.0	6.6 ± 1.1	6.4 ± 1.1
Maximum pain	7.9 ± 1.0	8.1 ± 1.1	7.7 ± 1.4
Patient history, n			
Musculoskeletal	23	29	29
Gastrointestinal	7	9	3
Respiratory	6	3	6
Cardiovascular	5	0	1
Neurologic	1	3	3
Immunologic	3	4	3
Genitourinary	1	6	1
Mental health, n			
Depression	13	12	15
Post-traumatic stress disorder	5	9	4
Panic disorder	8	9	3
Phobia disorder	6	9	9

All data are mean ± SD, unless otherwise stated.

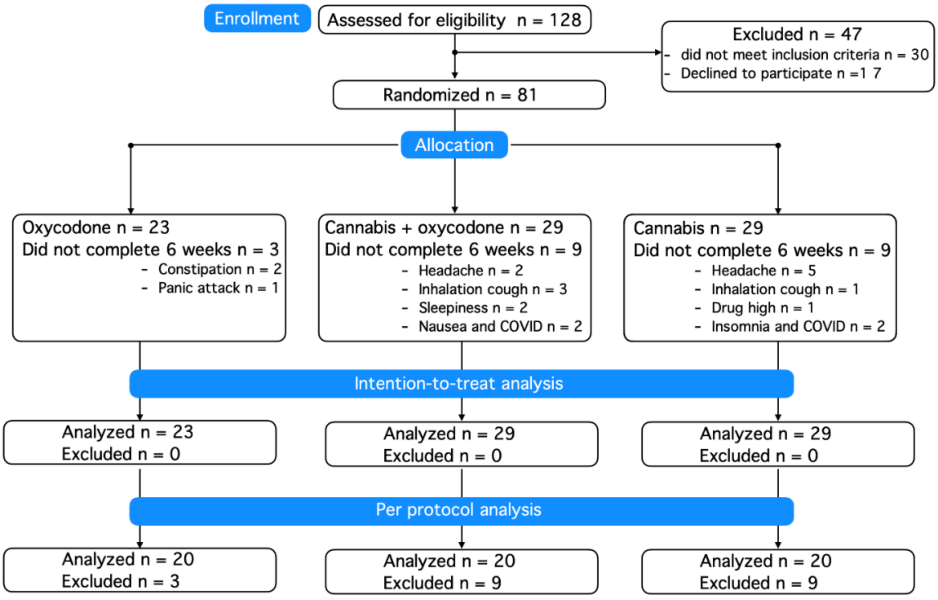

Figure 1. Consort flow diagram.

Eighty-one patients were randomized and treated, of which 21 (26% of treatment exposed participants) decided to end their consent to participate in the first 2-3 weeks of treatment due to the occurrence of AEs; see Kaplan-Meier curve (Fig. 2). Eighteen participants treated with cannabis (9 in each group, 31%) dropped out of the study because of, what we consider cannabis-related AEs such as headache, coughing upon inhalation, drug high, sleepiness or insomnia. In agreement with the protocol, all participants that dropped out were replaced such that 20 patients in each treatment successfully completed the trial. Drop outs did not differ among treatment groups (log-rank Mantel Cox test $p = 0.08$), but we argue that it approached significance given the small sample sizes per group, favoring oxycodone above treatments that included cannabis.

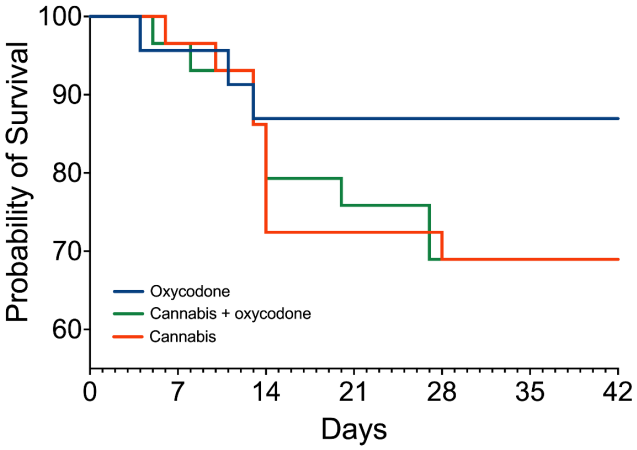

Figure 2. Survival curves: number of patients in the study. Blue line: oxycodone group; Orange line: cannabis group; Green line: combined cannabis and oxycodone group. In the oxycodone group 23 began treatment and three patients dropped out. In both other groups 29 patients started treatment and 9 patients dropped out. The numbers give the number of subjects in the trial for the three treatment arms.

7.4.1 Composite adverse event score

Intention-to-treat analysis

cAEs are given in Figure 3, panels A-C. The graphs show that the number of cAEs was higher in the first two weeks of treatment in the cannabis and cannabis/oxycodone groups with particularly high maximum cAE scores (8-10) and higher median scores. In the first 2 weeks of treatment, median AE scores ranged from 1-3 in the oxycodone, 2-5 in the oxycodone/cannabis and 2-3 in the cannabis groups. From day 14 on, median cAE scores over time were 2 (oxycodone), 1.5 (oxycodone/cannabis) and 1.5 (cannabis), with no difference in cAE scores among the three treatment arms (linear mixed model: $p = 0.97$).

Per protocol analysis

The results of the analyses are given in Figure 3, panels D-F, and show that the 60 patients that completed the study had median cAE values that ranged from 1-2 throughout the study period. Total cAE scores were oxycodone 91 ± 64 (mean ± SD); cannabis 72 ± 53; oxycodone combined with cannabis 76 ± 43. Mixed model analysis revealed that the scores over time were not different among treatment arms ($p = 0.70$). The different components of the cAE score contributed equally to the score with somewhat less constipation in the cannabis group and more drug high in the combination group. Most prevalent scores were sleepiness, headache,

insomnia and constipation (occurring in > 10% of patients; Table 2). Paranoia and hallucinations were scarcely reported by the participants and contributed <0.2% to the cAE; vomiting contributed 1% to the cAE. All patients tapered their treatment down at the end of the 6-week period, and no additional AEs related to withdrawal were reported by the patients.

Table 2. Components of the composite Adverse Event Score and distribution among treatments of the 60 subjects that completed the protocol

Component of score	Oxycodone	Oxycodone + cannabis	Cannabis
Dizziness	12	12	8
Sleepiness	24	20	20
Insomnia	16	23	17
Headache	14	23	21
Nausea	14	7	10
Vomiting	1	1	1
Constipation	15	8	13
Drug high	4	6	10
Hallucinations	0	0	0
Paranoia	0	0	0
Total	100	100	100

Data are percentage of total score for that specific treatment

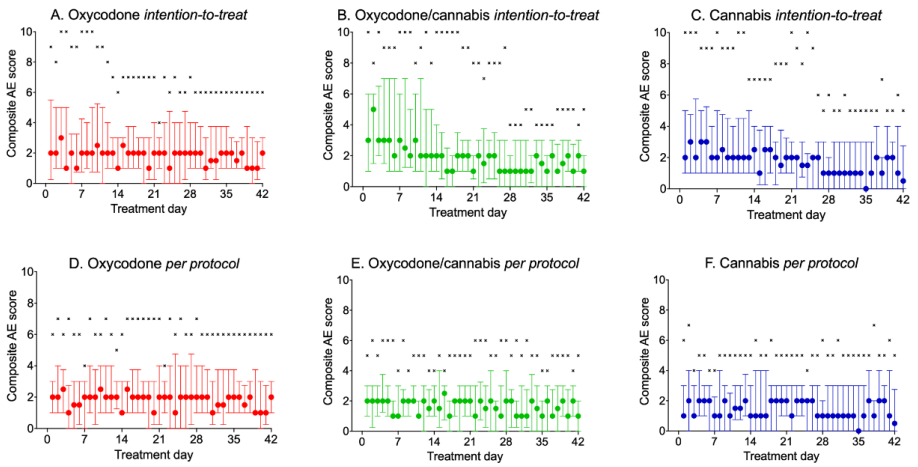

Figure 3. A-F: Daily composite adverse event score during the 42 days of treatment. A-C: intention-to-treat population; D-F: per protocol treatment. Circles median ± interquartile ranges. × maximum reported pain scores.

7.4.2 Pain relief

Median pain scores in the intention-to-treat group and in the per protocol group were not different among treatment arms (both analyses $p > 0.05$; Fig. 4). There was little change in pain scores over time in all three treatment arms. The per protocol data analysis showed that irrespective of treatment, about 50% of patients had a decrease in NRS of 1-point or more and 20% of 2 points or more. About 25 to 30% of patients had no clinically relevant analgesic benefit (NRS change<1) from any treatment, while 20-35% of patients that had an increase in pain score over time (median change +0.6 NRS-points, interquartile range 0.3-1.1 NRS-points). Among treatments, there were no differences in the responder rate distribution.

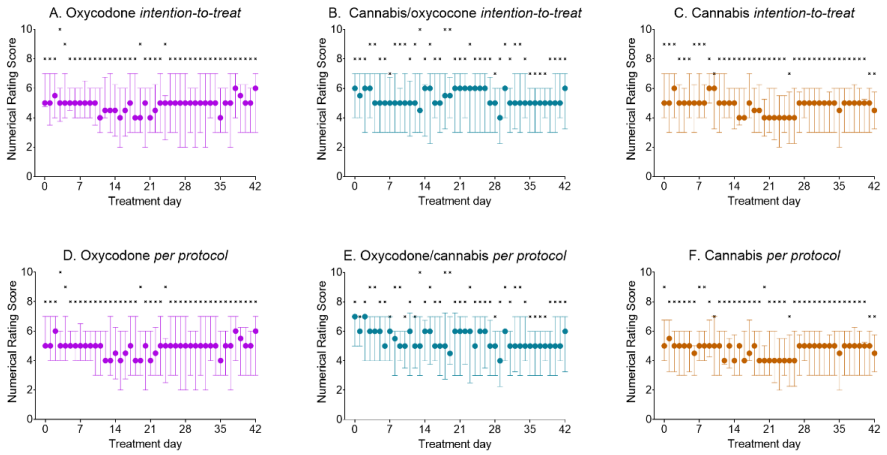

Figure 4. Daily composite pain scores. A-F: Daily composite pain scores during the 42 days of treatment. A-C: intention-to-treat population; D-F: per protocol treatment.. Circles median ± interquartile ranges. × maximum reported pain scores.

7.4.3 Medication use

The mean ± SD total number of oxycodone tablets consumed during the trial was 112 ± 37 or 3 tablets/day (median with range 1-4) in the oxycodone group *versus* 83 ± 40 in the combined oxycodone/cannabis group (2 tablets per day with range 0-3), or a difference of 28 tablets in the study (95% CI 3-53), which reflects a median 1 tablet difference per day (with 95% CI 0.2 to 1.5, $p = 0.02$). The mean number of total cannabis inhalation sessions were 101 ± 37 sessions (median 2 inhalations per day with range 1-4) in the cannabis arm *versus* 86 ± 35 inhalations (median 2 inhalations per day with range 1-4) in the combined oxycodone/cannabis arm, with a difference of 16 inhalations in the study (95% CI -7-39) which reflects a median

0 tablet difference per day (with 95% CI -1 to 0.2, p = 0.23). The total drug load in the combined arm was 169 (cannabis + oxycodone = 83 + 86). Figure 5 gives the medium number of tablets and inhalation sessions per group, depicting the up- and down-titration of oxycodone and cannabis in the three treatment groups. The difference in drug use between single and combined treatments (A *vs* C, and B *vs* D) is about one oxycodone dose and cannabis inhalation session per day. It also shows that tapering down occurred successfully in the last days before the end of the study.

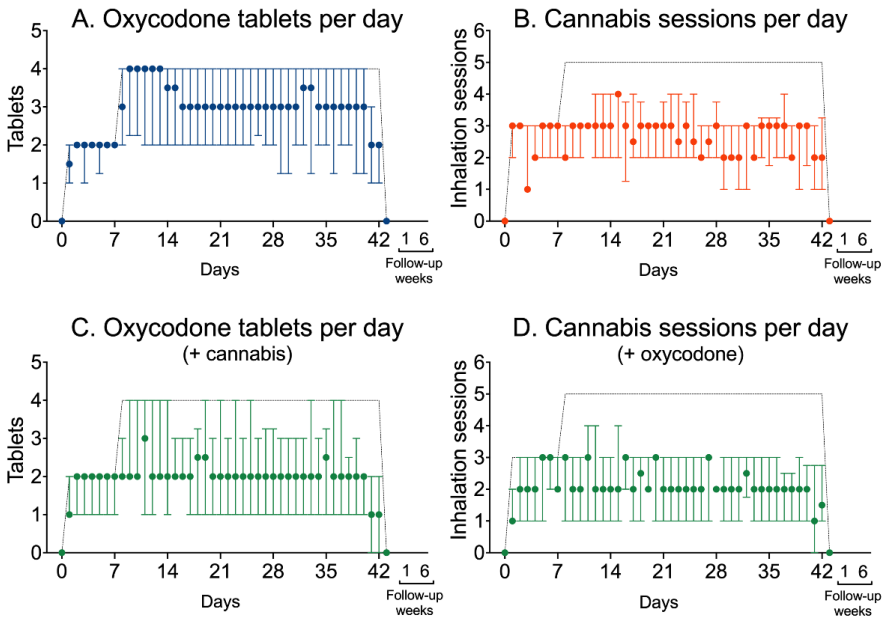

Figure 5. Medication per day. Use of oxycodone tablets and cannabis inhalation sessions in the three treatment groups. A. Median oxycodone tablets (± interquartile ranges) used per day in patients that just received oxycodone. B. Median number of inhalation sessions per (± interquartile ranges) in patients that just received cannabis. C. Median oxycodone tablets (± interquartile ranges) used per day in patients that additionally received cannabis. D. Median number of inhalation sessions per (± interquartile ranges) in patients that additionally received oxycodone. The broken lines depict the maximum allowed oxycodone doses and cannabis inhalation sessions.

7.4.4 Discussion

The main outcomes of our study are that in fibromyalgia patients treated with cannabis combined with oxycodone or just oxycodone or cannabis in a self-titration paradigm: (i) approximately 1 in 4 subjects dropped out of the study, mainly due the severity of AEs experienced from inhaled cannabis, irrespective of treatment group;

(ii) there were no significant differences in pain scores among treatments with 30% of the patients experiencing ≥1-NRS (but <2-NRS) pain reduction and 20% ≥2-NRS, while 50% of patients had no analgesic benefit from any treatment; (iii) the drug load increased in subjects treated with the combination of oxycodone and cannabis relative to either treatment alone; and (iv) patients titrated their treatment based on AEs and pain relief, an indication that patients dosed themselves based on the utility of treatment (where utility is defined as the maximization of the difference between analgesic effects and adverse effects).[16] Our findings challenge the belief that combining cannabis with an opioid reduces opioid consumption with lesser AEs. Nonetheless, our data do suggest benefit from cannabis in a small subset of patients that were able to endure the inhalation of cannabis and reported a reduction in pain scores of at least one point.

7.4.5 Adverse effects

The finding that 18 patients discontinued treatment (Fig. 2) indicates that a significant portion of our patients was not suited for pain management with cannabis. They not only experienced a high number of daily AEs, but the severity of symptoms was compelling enough to discontinue treatment within the first weeks of treatment. Particularly headache was severe and occurred in 12% of dropouts (Table 2). Despite the high number of dropouts, at this point we cannot exclude that there may possibly be a role for cannabis monotherapy in chronic pain management, because of its effectiveness and low number of AEs, however, in just a minority of patients. Since prediction of treatment outcomes is challenging, more research is needed to *a priori* identify which patients could benefit most from cannabis. Additionally, we acknowledge that there is the risk for cannabis use disorder, and consequently cannabis treatment should be applied with careful monitoring.

Our suggestion that combining oxycodone with cannabis would reduce the number of side effects compared to either treatment alone was not supported. This outcome may be attributed to the self-titration of study medication in which patients could adjust their drug consumption when side effects occurred too frequently or were more intense than acceptable. This challenges the traditional treatment paradigm that prescribes fixed daily doses, instead supporting a more flexible or adaptable dosing strategy, particularly for drugs like cannabis and opioids, known for their wide range of AEs.

7.4.6 Pain relief and drug load

The analgesic effect from the oxycodone-cannabis combination was comparable to that of either treatment alone (Fig. 4). This outcome was achieved with less

oxycodone consumption (reduction 26%) without affecting the number of cannabis inhalations significantly. Although the reduced oxycodone tablet intake is an important and relevant observation that is often pursued in clinical practice, the total drug load (cannabis+oxycodone) exceeded that of either treatment alone. Since these are two drug classes with a high potential of misuse and because of the absence of added benefit from their combination. We argue that our study does not simply support the concurrent use of cannabis and oxycodone for the management of chronic pain. Possibly, in patients that use oxycodone cannabis may be added to slowly taper down the opioid. However, further studies are needed to explore this issue.

7.4.7 Comparison with the literature

In line with our findings, various studies reported a high incidence of AEs from cannabis for treatment of chronic pain.[17,18] In contrast, a 2024 review on opioids and cannabis in chronic pain found both treatments moderately effective in pain relief, with cannabis causing fewer dropouts than opioids.[19] The discrepancy with our study may be related to the use of different cannabis varieties or differences in patient cannabis experience. Regarding the combined use of opioids and cannabis for chronic noncancer pain, a recent systematic review of retrospective studies and surveys concluded that cannabis produced a significant reduction in self-reported opioid consumption compared to patients that did not use cannabis.[9] These findings contrast ours, which we relate to the critical bias of included studies, the wide range in cannabis use (1.5 mg to 2 g), and study populations that were experienced cannabis users.

7.4.8 Study limitations

There were several study limitations that deserve discussion:

(i) Apart from the patients that discontinued participation, we remained uninformed on the intensity or severity of the subjectively experienced AEs. While this may be considered a caveat, we *a priori* reasoned that intensity is difficult to score for patients, particularly when multiple symptoms occur concurrently or when symptoms needed to be scored just once, at the end of the day, and would complicate the implementation of the study. It is our experience that patients more frequently complain about the occurrence of symptoms rather than about the intensity. Patients that remained in the study deemed the intensity of their symptoms acceptable, while those that dropped out deemed their adverse effects severe and unacceptable.

Moreover, using the prespecified cAE, we may have missed some adverse events.

(ii) The high number of dropouts in individuals that received cannabis introduces a potential bias, particularly when assessing subjective symptoms and pain relief. The absence of difference between the *per protocol* and intention-to-treat analysis suggests little influence of drop-outs on the study outcomes. This was further substantiated by a sensitivity analysis that showed that with the number of dropouts in our study the power to detect differences among study arms had dropped to about 80%. Additionally, the high number of dropouts indicates that in some patients the choice for cannabis is unwise and alternatives should be probed.

(iii) We designed a cAE score with fixed symptoms. While we allowed the reporting of other symptoms, we may have missed some symptoms that were not part of the current scoring system. The cAE score was made up of symptoms that we expected to occur from opioid (*e.g.* constipation, nausea), cannabis (*e.g.* drug high, hallucinations, paranoia) or both treatments (dizziness, sleepiness). Interestingly, the distribution of side effects did not seem to diverge among treatments.

(iv) Adding a placebo control would have provided a clearer baseline for evaluation of the combination therapy's effectiveness. The absence of a placebo group may have affected the outcome of our study, although we argue that by comparing three distinct treatments in a similar fashion, any placebo (or nocebo) effect may have been present among all three treatment groups. Additionally, adding a placebo is difficult in psychedelic drug research, as full blinding seems difficult and items such as expectation may affect the study outcome. This may possibly be reduced by using active placebos.[20]

(v) The study population was predominantly female, which reflects the disease sex distribution. However, this limits the generalizability of ours study beyond the female sex and beyond fibromyalgia.

(vi) We excluded patients with prior cannabis consumption to standardize our study population. Therefore, this further limits the extrapolation of our study results to the broader chronic pain population. Possibly, patients with prior experience with cannabis consumptions would have had fewer adverse events compared to our cannabis-naïve population. This may have overestimated the effect of cannabis on adverse outcomes and the drop-out rate in our current population.

(vii) cAE and pain scores were analyzed from days 14-42 of treatment. In order to asses how this affected our study outcome, we *post hoc* performed

analyses of the complete 52 days of the study. Although this did not affect the outcome, the large number of dropouts in all three arms of the study during this period made us decide to exclude these study days in the main analyses.

7.5 CONCLUSIONS

In this relatively small open-label trial in patients with chronic pain from fibromyalgia that is best considered exploratory, we showed that self-titration with oxycodone, cannabis or their combination, was successfully completed in 75% of the study population. In 25%, AEs were intolerable and patients discontinued participation in the first 2-3 weeks of the trial. Importantly, patients treated with cannabis dropped out of the study at a three-times higher incidence (31%) than participants randomized to just oxycodone (12%). Irrespective of treatment, the responder rate of patients that completed the 6-week treatment period did not differ among treatment groups. The combination of oxycodone and cannabis did not lead to fewer AEs or to a decrease in total drug load, indicating that this combination may not offer additional benefits and could even carries a greater risk of harm due to the abuse and toxicity potential of these two drugs compared to just one drug. Still a small subset of patients who did tolerate cannabis self-titration and achieved an acceptable efficacy with limited side effects (median cAE score 2). More research is needed in larger sample sizes with inclusion of placebo groups and with a proper characterization of specific patient phenotypes to predict the tolerance to cannabis therapy and therapeutic effectiveness of cannabis for the management of chronic pain. For now, we would argue that the use of cannabis is best restricted as last resort in patients with therapy-resistant chronic pain with careful monitoring of therapeutic effect and AEs. Finally, we would like to stress once more that opioids are not the recommended treatment for chronic pain in fibromyalgia patients. See for treatment guidelines references 11, 12 and 13.[11-13]

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