Cannabidivarin for HIV-Associated Neuropathic Pain: A Randomized, Blinded, Controlled Clinical Trial

Luca Eibach[1], Simone Scheffel[1,2], Madeleine Cardebring[1,3], Marie Lettau[1,6], M. Özgür Celik[1], Andreas Morguet[4], Robert Roehle[5] and Christoph Stein[1,*]

HIV remains a major burden to the health care system and neuropathic pain is the most common neurological complication of HIV infection. Because current treatment strategies often lack satisfying pain relief, cannabinoids (CBs) are discussed as a new option. We investigated cannabidivarin (CBDV) as treatment for HIV-associated neuropathic pain. We conducted a randomized, double-blind, placebo-controlled crossover study. Patients underwent two successive treatment phases (4 weeks each) and were treated with CBDV (400 mg/day) or placebo in a randomized order. A 3-week washout phase was designed to eliminate potential carry-over effects. Patients were followed up for 3 weeks after the end of the second treatment phase. The primary end point was pain intensity on an 11-point numeric rating scale, recorded in a diary. Secondary end points were additional pain medication, pain characteristics, and quality of life. We included 32 patients. The mean pain intensity under CBDV was 0.62 points higher compared with placebo (P = 0.16, 95% confidence interval −0.27 to 1.51). CBDV did not influence the amount of additional pain medication, pain characteristics, or quality of life. The incidence of adverse events was similar during both treatments. No suspected unexpected adverse reactions occurred during either treatment. CBDV was safe but failed to reduce neuropathic pain in patients with HIV. This may be explained by a lack of CB receptor activation, as indicated by preclinical experiments. Although a larger patient number might be desirable, we would not expect a change in the conclusions because the present differences are far from statistical significance. Therefore, we would currently not consider CBDV as a clinically meaningful treatment option for neuropathic pain.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Pain relief in patients with HIV-associated neuropathic pain is often unsatisfying but cannabinoids (CBs) have shown promising results in preclinical studies.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ Can pain relief be achieved by the novel phytocannabinoid cannabidivarin (CBDV) in patients with HIV-associated neuropathic pain?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ CBDV was safe but failed to improve neuropathic pain or quality of life in patients with HIV.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Despite encouraging preclinical data, CBDV is not a promising substance for treatment of patients with HIV-associated neuropathic pain. We presume that clinical pain relief is unlikely to be achieved without activation of CB receptors.

Approximately 7–8% of the general population have neuropathic pain, defined as "pain that arises as a direct consequence of lesions or diseases affecting the somatosensory system."[1,2] Chronic neuropathic pain impairs quality of life and negatively affects the patients' social relationships.[3] Among various diseases that can underlie neuropathic pain, HIV infection belongs to the most prevalent.[4] Despite the development of highly effective antiretroviral therapy, HIV remains a major burden to the health system.[5]

HIV-associated neuropathic pain usually occurs together with distal sensory neuropathy with symptoms of burning or dysesthesia in combination with numbness in stocking-like or glove-like distribution,[6] and may be caused by the inflammatory effects of HIV-infected macrophages and other neurodegenerative mechanisms.[6,7]

[1]Department of Anesthesiology, Charité Universitätsmedizin, Campus Benjamin Franklin, Berlin, Germany; [2]SteriPharm Pharmazeutische Produkte, Berlin, Germany; [3]Vivantes Klinikum Kaulsdorf, Berlin, Germany; [4]Department of Cardiology, Charité Universitätsmedizin, Campus Benjamin Franklin, Berlin, Germany; [5]Institute of Biometry and Clinical Epidemiology, Coordinating Center for Clinical Studies, Berlin Institute of Health, Charité Universitätsmedizin, Berlin, Germany; [6]Present address: Medizinische Klinik Rheumatologie und Deutsches Rheumaforschungszentrum, Charité Universitätsmedizin, Berlin, Germany. *Correspondence: Christoph Stein (christoph.stein@charite.de)

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Furthermore, antiretroviral drugs, mainly dideoxynucleoside reverse transcriptase inhibitors, can cause mitochondrial and nerve damage[7] so that they are no longer recommended.[8] Despite novel, more effective, and less neurotoxic antiretroviral drugs, the prevalence of neuropathic pain in HIV-infected patients is still high and causal treatment is not available.[6] Although treatment of chronic neuropathic pain should be based on both pharmacological and interdisciplinary nonpharmacological approaches (e.g., behavioral, physical, and/or occupational therapy),[4] pharmacological therapy often predominates. Antidepressants, anticonvulsants, and opioid analgesics are medications of choice.[9] However, they often lack efficacy[4] and are limited by side effects, such as respiratory depression, addiction, and sedative effects,[10] resulting in extensive additional costs and reduced quality of life.[3,11,12]

Endocannabinoids (e.g., 2-arachidonylglycerol and anandamide) influence the transmission of pain signals by acting on cannabinoid (CB)-receptors 1 and 2.[13] Some exogenous cannabinoids (CBs) have shown promising results in the treatment of neuropathic pain but they were limited by complicated dosing of smoked cannabis and side effects like nausea or drowsiness.[14–16] Therefore, improved CB and opioid analgesics are being developed.[9,13,17,18]

In this study, we investigated cannabidivarin (CBDV) a novel phytocannabinoid derived from the *Cannabis sativa* L. plant, in patients with HIV-associated neuropathic pain. Using a double-blind crossover trial design, we assessed pain, side effects, and quality of life, and sought to correlate treatment responses to the patients' genotype.

METHODS

Study design

Data were collected from January 1, 2017, to January 8, 2019. We conducted a randomized, placebo-controlled, double-blind crossover phase II trial in a single-center outpatient setting. All patients received both treatments (CBDV and placebo) in two successive phases. The order of treatments (CBDV-placebo (C-P) or placebo-CBDV (P-C)) was allocated by chance (randomized). Each patient was monitored for 13 weeks. After the screening phase, baseline values on pain scales, questionnaires, and medications were recorded during a 1-week phase (**Figure 1**). This was followed by 4-week treatment phase A with either placebo or CBDV. A subsequent 3-week washout phase was included to eliminate potential carry-over effects. The duration of the washout phase was based on data showing an accumulation of cannabinoids (CBs) in fatty tissue resulting in a half-life of about 5 days after long-term oral administration.[19] Thereafter, another 1-week baseline phase ensued, followed by treatment phase B. Patients were then followed up for another 3 weeks. Throughout the study, the patients documented data in diaries (see also study protocol in **Supplementary Materials**).

Study participants

Participants were recruited through personal contacts to physicians and patient-advocacy groups in the greater Berlin area, as well as by advertisement in the Berlin public transportation system. Before inclusion, subjects were screened for age (18–65 years), vital signs, and pain intensity (≥ 4 on an 11-point numeric rating scale (NRS)). The diagnosis of HIV-associated sensory neuropathy was confirmed by a clinician (C.S., M.C., or M.L.) based on patient history, the Douleur Neuropathique 4 interview (DN4i), and the Clinical HIV-associated Neuropathy Tool.[20,21] Exclusion criteria were pregnancy and lactation, major psychiatric conditions, severe diseases of the central nervous system, hepatic, renal, or cardiovascular diseases, or use of conventional cannabinoids (CBs), examined by blood test. Electrocardiograms were recorded on the day of screening and analyzed for abnormalities by an experienced cardiologist (A.M.). Infection with hepatitis virus B or C and AIDS-defining diseases were debarred by consulting HIV specialists. The use of concomitant analgesics (including antidepressants and anticonvulsants) as needed was permitted throughout the study. Standard laboratory values (full blood count, liver function tests, electrolytes, glucose, urea, cholesterol, creatinine, creatinine kinase, protein, and international normalized ratio) were recorded on the day of screening and during the trial.

Outcome measurements

The primary outcome was pain intensity measured thrice a day (8:30 AM, 1:00 PM, and 7:00 PM) by an 11-point NRS (0 = no pain to 10 = worst pain imaginable), as documented in the patient diary. For each day, the arithmetic mean of the three NRS scores was determined. According to several previous studies on neuropathic pain,[22,23] a decrease of mean NRS values by at least 20% between the last day of baseline measurement and the last day of treatment was defined as a clinically relevant effect (responder). The number of responders and nonresponders to each treatment was determined. Secondary end points were pain characteristics, quality of life, and sleep, measured by questionnaires. We used painDETECT,[24] the Brief Pain Inventory,[25] and the DN4i[21] for evaluation of pain intensity and pain characteristics, the Hospital Anxiety and Depression Scale[26] to evaluate anxiety and depression, and the 36-Item Short Form Survey,[27] the Patient Global Impression of Change,[28] and the Insomnia Severity Index for quality of life and sleep,[29] respectively. All questionnaires were applied on the last day of each baseline phase and on the last day of each treatment phase, except Patient Global Impression of Change, which was only used at the end of each treatment phase. Concomitant medication and side effects were recorded in the patient diary. For the analysis of concomitant pain medication, we used the Medication

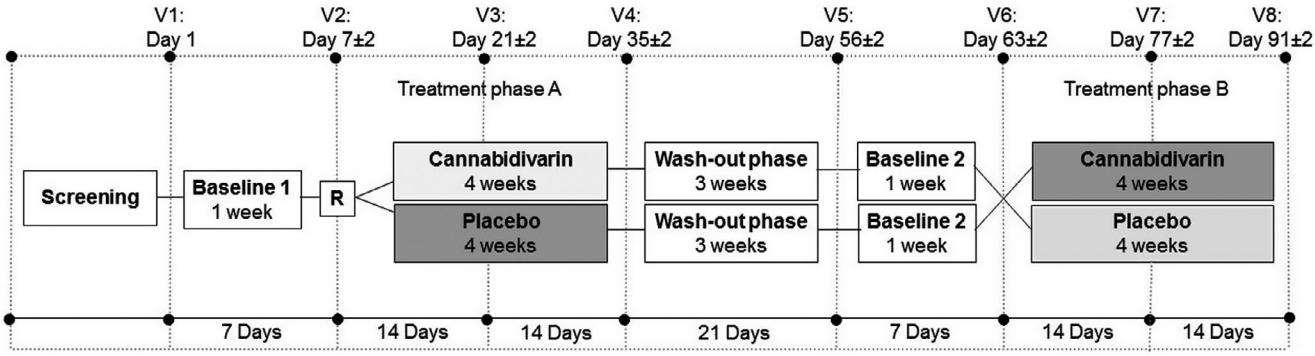

Figure 1 Study design. R, randomization; V, visit.

Quantification Scale (MQS) in its third version, which assigns a score (on an unlimited scale) based on the detrimental effects and dose of each pain medication.[30] For analysis of side effects, patients were asked to document any adverse or unusual events. These were discussed with a study physician at each visit. For standardized documentation, we used paper-based tables and classified the events with the Common Terminology Criteria for Adverse Events, version 4.03.

Randomization, allocation concealment, and blinding

Randomization to the sequence of treatments occurred in blocks of four by use of paper-based, computer-generated random lists, which were stored in a locked cabinet. Included patients were pseudonymized by generating a serial number (ID). Allocation to the treatment sequence was documented and kept in sealed envelopes. All patients and staff involved in patient contacts and assessment of outcomes were blinded until the end of the study.

Monitoring

Two independent monitors conducted unblinded monitoring of patient safety and adherence to good clinical practice principles throughout the trial.

Investigational Medicinal Products

The active agent and placebo, both dissolved in sesame oil, were identically appearing and tasting solutions. The Investigational Medical Products was packaged in amber-glass bottles by GW Pharmaceuticals. All bottles were subject-specific and marked with the patient ID. The bottles with active agent contained 50 mg CBDV/mL. Patients were instructed to use 8 mL of the solution orally every morning at 9 AM, corresponding to 400 mg CBDV in the verum treatment phase (for detailed information see **Table S1**). The dose was chosen based on preclinical and clinical phase I studies, showing that daily doses between 200 and 800 mg were well-tolerated.[31]

Inactivation of HIV in blood samples, DNA isolation, and genetic analysis

Blood samples were obtained during the last visit from 28 patients who gave consent for genetic analysis. Five mL of peripheral venous blood was mixed with 15 mL of red cell lysis solution (Epicentre R) and incubated at room temperature for 10 minutes. After centrifugation, supernatant was discarded, and the pellet was dissolved in 7.5 mL tissue and cell lysis solution (Epicentre R). The solution was kept at 65°C for 1 hour for inactivation of HIV and cell lysis. Samples were then stored and transported at −20°C until genotyping by deCODE Genetics (Reykjavik, Iceland). Whole genome sequencing was performed by the Infinium Global Screening array (GSA24, Illumina).

Statistics

Sample size was calculated by nQuery Advisor 7.0 based on the primary end point (NRS scale) and the crossover study design. According to previous literature, a pain reduction by 20% upon verum compared with placebo and a common SD for the period differences of 2.5 seemed to be achievable and would have been clinically meaningful.[22,23,32] We calculated that 21 patients per sequence group were sufficient to show this effect (e.g., a reduction of 20% from 6 points to 4.8 points) with a power of 85% and a two-sided type I error of 0.05 using a paired *t*-test for 2 × 2 crossover designs. To account for an estimated 15% dropouts, we aimed at a total of 50 patients. Because some guidelines define higher pain reductions as clinically relevant,[33] we also provide 30% and 50% pain reduction analyses to allow our data to be used in data syntheses.

Statistical analysis was based on the intention-to-treat principle (i.e., every patient who started treatment and had at least one post-baseline measurement of the primary end point was included in the full set for the efficacy analysis). Continuous variables are shown as mean, SD, and range, whereas categorical parameters are given as absolute and relative frequency. For the continuous end points, first, the difference between sequence-specific baseline and the value after treatment was calculated. Then, for each individual the difference between the two treatment effects (C-P) was determined. A paired *t*-test taking period effects into account was used for comparing the two treatments. In case of non-normality of data distribution, a nonparametric version was applied instead. The 95% confidence intervals (CIs) were calculated for the treatment effects. Further, for the primary end point, a random subject intercept mixed model was calculated. This model used the change of NRS values from phase baseline to post-treatment as dependent variable, and treatment, phase, and NRS phase baseline value as independent variables. All *P* values resulting from the analyses have to be considered as nonconfirmatory using a cutoff of 0.05. All analyses were done using R (version 3.5.0)[34] (see also statistical analysis plan in **Supplementary Materials**).

Study approval

Written informed consent was obtained from all participants prior to inclusion in the study. The trial protocol, patient information, and informed consent sheets were approved by the ethics committee of the state regulatory authority Berlin (Landesamt für Gesundheit und Soziales; 15/0255 EK 13) and the German Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte; 61-3910-4040377). The CONSORT guidelines and checklist, good clinical practice principles, and the Declaration of Helsinki were strictly followed. The study was registered at EudraCT (https://www.clinicaltrialsregister.eu/) under number 2014-005344-17.

RESULTS

Patient population

From January 2015 to September 2018, a total of 194 patients were contacted by email or phone, of which 55 were screened in the study center. Screening was terminated as planned at the end of financial support. Thirty-four patients gave informed consent and were assigned a patient ID. The data of two patients could not be used for final efficacy analysis due to missing data or screening failure but were included in the safety population (for more information see **Figure S1**). Characteristics of the remaining 32 patients included in the efficacy analysis are shown in **Table 1**. All patients met the inclusion criterion of a positive DN4i (≥ 3) and Clinical HIV-associated Neuropathy Tool. Of the remaining 32 patients, 4 dropped out during the study but were not excluded from analysis. Patients were randomized to receive CBDV in treatment phase A followed by placebo in treatment phase B (C-P), or placebo in phase A followed by CBDV in phase B (P-C).

Primary end point

Overall, mean pain intensity (NRS) at the end of CBDV treatment was 0.62 points higher compared with placebo; this difference was not significant (P = 0.16, 95% CI −0.27 to 1.51) (**Figure 2**, **Figure 3**, **Table S2**). The mixed model provided very similar results (difference 0.63, 95% CI −0.05 to 1.32). The differences between mean NRS at the end of the treatment and baseline were not statistically significant for any substance or treatment phase (**Figure 3**). The mean NRS value at the end

Table 1 Data on day of initial screening

		Treatment sequence CBDV-Placebo	Treatment sequence Placebo-CBDV	Total
Male, *n*		16	15	31
Female, *n*		0	1	1
Age, years	Mean (SD)	52.31 (8.06)	48.31 (9.62)	50.31 (8.96)
	range	36–65	31–65	31–65
NRS score (0–10)	Mean (SD)	6.12 (1.15)	6.44 (1.59)	6.28 (1.37)
	range	4–8	4–9	4–9
DN4i (0–7)	Mean (SD)	5.19 (1.17)	5 (0.89)	5.09 (1.03)
	range	3–7	4–6	3–7
Duration of pain, years	Mean (SD)	16.47 (7.91)	9.94 (8.77)	13.1 (8.87)
	range	2–30	1–27	1–30
Duration of HIV infection, years	Mean (SD)	24.88 (9.17)	17.81 (10.81)	21.4 (10.2)
	range	3–33	2–32	2–33
On cART, *n*		16	15	31

cART, combined antiretroviral therapy; CBDV, cannabidivarin; DN4i, Douleur Neuropathique 4 interview; NRS, Numeric Rating Scale.

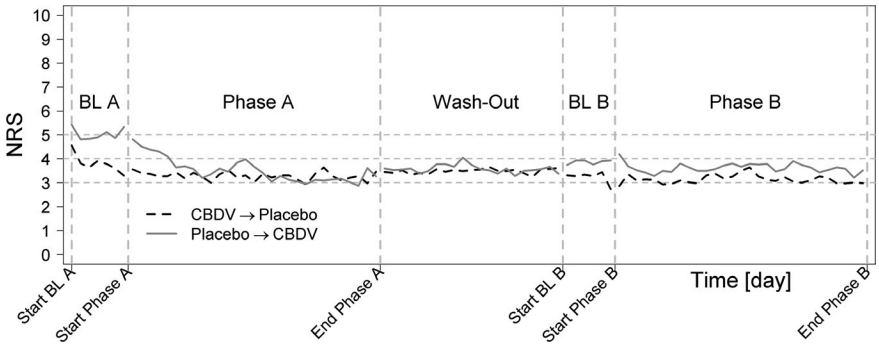

Figure 2 Pain intensity over time. Descriptive presentation of pain intensities per day (means) by treatment sequence. Cannabidivarin (CBDV)-placebo (black, broken line); placebo-CBDV (grey, continuous line). BL, baseline; NRS, Numeric Rating Scale.

of follow-up (3 weeks after end of treatment phase B) was 2.74 (SD = 1.47) in the C-P group and 3.67 (SD: 2.62) in the P-C group. During CBDV treatment, 9 patients experienced a mean pain reduction of at least 20% and were therefore classified as CBDV responders. By the same criteria, 19 patients were classified as placebo responders. Based on a 30% pain reduction, 6 patients were CBDV-responders and 13 patients responded to placebo. A 50% pain reduction was experienced by 1 patient under CBDV and by 9 patients under placebo.

Secondary end points

No statistical differences between CBDV and placebo were detectable by any of the questionnaires analyzing pain characteristics, sleep quality, subjective impression of change, or quality of life (**Table 2**, **Figure 4**). No significant changes in specific parameters in the painDETECT questionnaire were detectable. Overall, the intake of additional pain medication, measured by the MQS, was not significantly different between CBDV and placebo (median treatment effect of CBDV compared with placebo = 0, $P = 0.52$, 95% CI −0.05 to 2.85; nonparametric rank sum test; **Figure 5**).

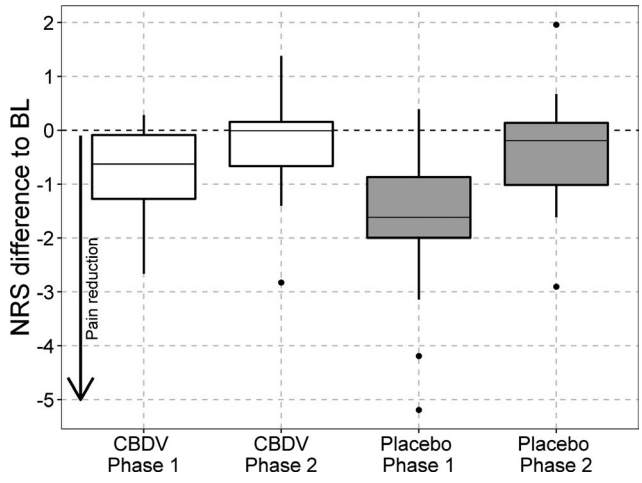

Figure 3 Pain intensity difference by treatment and phase. Differences (medians) between numeric rating scale (NRS) values on the last day of cannabidivarin (CBDV; white) and placebo (grey) phases and baseline (BL) values, respectively. Negative values indicate pain reduction; bars indicate minimum and maximum values; dots indicate values outside of 1.5* interquartile range (paired *t*-test; $n = 32$).

Table 2 Effects of CBDV vs. placebo assessed by questionnaires

Questionnaire (score range)	Effect CBDV vs. placebo
painDETECT (0–38)	−0.84 (*P* = 0.53, 95% CI −3.59 to 1.91)
DN4i (0–7)	−0.50 (*P* = 0.18, 95% CI −1 to 0.50)
BPI (pain intensity) (0–10)	+0.23 (*P* = 0.76, 95% CI −0.63 to 1.25)
BPI (influence on daily living) (0–10)	−0.35 (*P* = 0.22, 95% CI −1.36 to 0.43)
HADS (anxiety) (0–21)	−0.60 (*P* = 0.51, 95% CI −2.44 to 1.24)
HADS (depression) (0–21)	0 (*P* = 0.91, 95% CI −1.50 to 1.50)
ISI (0–28)	−1.50 (*P* = 0.24, 95% CI −5.50 to 1)
PGIC (0–7)	−0.50 (*P* = 0.26, 95% CI −1.50 to 0.50)

painDETECT and DN4i: higher values indicate presence of neuropathic pain; PGIC: higher values indicate a subjective improvement; all others: lower values indicate lower impairment. Paired *t*-tests, see Methods.
BPI, Brief Pain Inventory; CBDV, cannabidivarin; CI, confidence interval; DN4i, Douleur Neuropathique 4 interview; HADS, Hospital Anxiety and Depression Scale; ISI, Insomnia Severity Index; PGIC, Patient Global Impression of Change.

After CBDV treatment, the differences in MQS values between baseline and end of treatment were + 1.13 (SD = 7.13) in the C-P group and −0.16 (SD = 0.61) in the P-C group. After placebo treatment, these differences were + 0.11 (SD = 3.79) and −1.87 (SD = 5.26) in the C-P group and P-C group, respectively.

Adverse events

Thirty-one patients (91.2%) experienced at least one adverse event (AE) during CBDV treatment; and 27 patients (79.4%) had at least one AE during placebo. During each treatment (CBDV or placebo), nine patients (26.5%) experienced an AE that was considered to be related to study medication (**Table S3**). One serious AE (acute myocardial infarction) was recorded during CBDV treatment but was judged as not related to study medication. This patient (male, 62 years) had the following cardiovascular risk factors: history of arterial hypertension, transient ischemic attack, pulmonary embolism, and factor-V-Leiden mutation. The most common AEs were diarrhea and dry mouth (3 cases during each treatment; **Table S3**). The incidence of AEs was similar in both treatment phases. All AEs were of low or moderate severity; one patient withdrew study participation due to an AE (cough) during CBDV treatment. This was considered related to treatment. No clinically relevant or medication-related changes of laboratory values were noted.

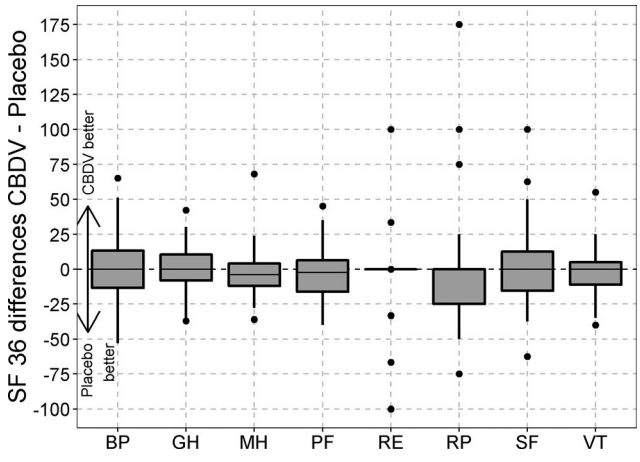

Figure 4 Treatment effects on quality of life. Differences (medians) between cannabidivarin (CBDV) and placebo effects as measured by SF-36. Bars indicate minimum and maximum values; dots indicate values outside of 1.5* interquartile range (paired *t*-test; *n* = 32). BP, bodily pain; GH, general health; MH, mental health; PF, physical functioning; RE, role emotional; RP, role physical; SF, social functioning; SF-36, 36-Item Short Form Survey; VT, vitality.

Genetic analysis

Samples from 28 patients who gave consent to genetic analysis were genotyped using the Infinium Global Screening array (GSA24; Illumina), and whole genome sequencing was performed on this subset of patients by deCODE Genetics (Reykjavik, Iceland). The small sample size did not allow a meaningful genomewide association analysis of response. However, these data may have utility in future meta-analysis efforts, and can be queried for the role of individual markers identified in other studies.

DISCUSSION

CBDV failed to reduce neuropathic pain intensity in patients with HIV. Additionally, we could not observe any statistically or clinically significant effects on use of supplementary pain medication, specific pain characteristics, or quality of life. CBDV and placebo produced similar rates of AEs, which were of mild to moderate severity.

According to data on CB receptor knock-out mice and pharmacological studies, the mechanisms underlying analgesic effects of CBs are thought to be based on the activation of CB1 and/or CB2 receptors, leading to an inhibition of pain signal transmission and/or anti-inflammatory effects.[13,35,36] This may either be achieved by exogenous CBs or by inhibiting enzymes degrading endocannabinoids (fatty acid amide hydrolase and/or monoacylglycerol lipase). Costa *et al.* also showed that antinociception can be produced by a CB re-uptake inhibitor in rats.[37] In addition, effects of phytocannabinoids not primarily activating CB receptors have been described.[36]

CBDV is mainly known for its anticonvulsant effects.[38] Limited preclinical data indicated the occurrence of antinociceptive effects without binding to CB receptors.[31] Antinociceptive effects of CBs not activating CB receptors were observed in animal studies[39] but not in humans so far. Different mechanisms of action were hypothesized, such as inhibition of diacylglycerol lipase-α,[40] another enzyme influencing endocannabinoid. Some groups observed an activation of transient receptor potentials[40] and postulated that this activation could lead to desensitization of sensory neurons.[41]

To evaluate clinical effects, we assessed both pain intensity and the amount of supplemental pain medication. A dose reduction

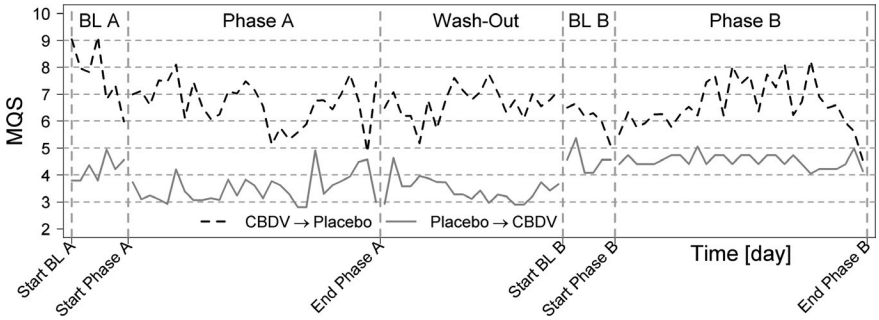

Figure 5 Medication quantification scale (MQS) values over time. Descriptive presentation of MQS values per day (means) by treatment sequence. Cannabidivarin (CBDV)-placebo (black, broken line); placebo-CBDV (grey, continuous line); baseline (BL); *n* = 32.

of additional pain medication can minimize detrimental side effects and can therefore be useful. CBDV, however, did not significantly change pain intensity or the use of additional pain medication as compared with placebo. Potentially promising effects may be assumed in **Figure 5** but should be considered visually misleading because real differences on the unlimited MQS were small and not statistically significant. We also examined whether CBDV can influence pain characteristics, such as burning sensation, numbness, or heat hyperalgesia. Due to the possible involvement of TRPV1,[40] a receptor that is responsible for heat sensation,[42] one might assume that CBDV can alleviate burning sensations in patients with neuropathic pain. In the painDETECT questionnaire, however, CBDV did not influence any specific pain characteristics. To our knowledge, this is the first study investigating the influence of CBDV on such parameters.

Overall, CBDV was ineffective in our trial. This is in line with recent extensive meta-analyses that did not detect clinically relevant analgesic effects of CBs in humans with chronic noncancer pain.[14,43] The analysis by Stockings *et al*. included all CBs, all study designs, considered all outcomes recommended by the IMMPACT group, and it assessed the clinical relevance of these findings.[14] In our study, a notable (but statistically nonsignificant) pain reduction was observed in patients receiving placebo during the first phase (P-C) and a difference between the groups was visible at baseline A (**Figure 2**). However, on the day of screening, the NRS scores were quite similar (**Table 1**). Because patients were randomized and did not receive any test substances before baseline A, this NRS difference was due to chance. Another NRS difference is visible in group P-C between baselines A and B (**Table S2**). To account for baseline variations in the statistical analysis, we included sequence-specific baseline values into a linear mixed model. It is conceivable that patients who were not treated sufficiently for pain before entering our study benefitted psychologically due to the enhanced attention in the setting of a clinical trial. Similar findings were reported in several previous studies and meta-analyses on neuropathic pain in patients with HIV.[44–46] This underlines the importance of a multidisciplinary approach, including psychotherapy, to treat chronic pain.

Chronic pain negatively influences many other facets of the patient´s life according to the biopsychosocial model of pain.[3,12,47] CBs are known to influence emotional processes. For example, the CB receptor agonist Δ9-tetrahydrocannabinol may reduce the unpleasantness but not the intensity of pain.[48] We did not ask our patients about previous use of CBs. However, CBDV failed to improve any of these features in the current study. Again, this is in agreement with previous meta-analyses that did not find significant impacts of CBs on physical or emotional functioning in patients with chronic noncancer pain.[14]

CBDV does not bind to CB-receptors[31,38] and therefore should not show typical CB receptor-mediated psychotropic side effects, such as euphoria, reduced anxiety, or feeling "high,"[49] consistent with our findings. Because the most common side effects (diarrhea and dry mouth) did not differ between CBDV and placebo, we do not consider these AEs related to CBDV treatment. However, they could be associated with the sesame oil solution. We only observed side effects of low to moderate severity and only one patient withdrew due to such effects. For a more detailed analysis, a larger number of patients may be advantageous.

One serious AE (myocardial infarction) occurred during treatment with CBDV but was not considered related to CBDV. There are data supporting increased cardiovascular risk due to cannabinoids, but these data suggest a CB-receptor mediated mechanism.[50] CBDV and its major metabolites lack appreciable affinity and functional activity at the CB1-receptor[38] and neither clinical nor preclinical data point out any increase in cardiovascular risk. Therefore, the available information suggests that an association between CBDV and myocardial ischemia is unlikely.

We were able to obtain blood samples from most patients, but this sample size was not sufficient for a meaningful genomewide association study regarding treatment responses. However, these data are available upon request and may have utility in future meta-analysis efforts.

The time frame for patient inclusion was limited by the end of financial support. Due to additional, unexpected recruitment difficulties (many patients lost interest because we could not offer a satisfying remuneration), we could only enroll 16 patients per treatment sequence group instead of a planned sample size of 21. Although a larger patient number might have been desirable, we would not expect a marked change in the conclusions because the present results are far from statistical significance. Even the lower border of the 95% CI of the mean differences in NRS score does not promise any clinical relevance.

To conclude, this study showed that CBDV did not elicit more adverse side effects than placebo but failed to alleviate neuropathic

pain or associated parameters in patients with HIV. We presume that activation of CB receptors is necessary for significant analgesia. This was the first study investigating CBDV for neuropathic pain and further research with larger numbers of patients and possibly other types of neuropathic pain is desirable. However, because our results did not reveal any significant differences, we would not consider CBDV a clinically meaningful treatment option for HIV-associated neuropathic pain.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

L.E., R.R., and C.S. wrote the manuscript. S.S., L.E., and C.S. designed the research. L.E., S.S., M.C., M.L., Ö.C., A.M., and C.S. performed the research. R.R., L.E., and C.S. analyzed the data.

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