Recent qualitative systematic review of the effectiveness of cannabinoids in the management of pain advised against their widespread introduction into clinical practice because of limited relative efficacy in acute pain and common adverse effects. However, it was suggested that cannabinoids may have some beneficial effect in spasticity and in neuropathic pain, for which a therapeutic need is greater than in postoperative pain. In addition, the authors stated that new safe and effective agonists at the cannabinoid receptors may dissociate therapeutic effects from psychotropic liabilities of cannabis. CT-3 potentially possesses the efficacy to treat neuropathic pain and spasticity worthwhile.

1',1'Dimethylheptyl-$\Delta^8$-tetrahydrocannabinol-11-oic acid (CT-3), a potent analog of THC-11-oic acid, produces marked antiallodynic and analgesic effects in animals without evoking the typical effects described in models of cannabinoids. Therefore, CT-3 may be an effective analgesic for poorly controlled resistant neuropathic pain.

**Objective**
To examine the analgesic efficacy and safety of CT-3 in chronic neuropathic pain in humans.

**Design and Setting**
Randomized, placebo-controlled, double-blind crossover trial conducted in Germany from May-September 2002.

**Participants**
Twenty-one patients (8 women and 13 men) aged 29 to 65 years (mean, 51 years) who had a clinical presentation and examination consistent with chronic neuropathic pain (for at least 6 months) with hyperalgesia (n=21) and allodynia (n=7).

**Interventions**
Patients were randomized to two 7-day treatment orders in a crossover design. Two daily doses of CT-3 (four 10-mg capsules per day) or identical placebo capsules were given during the first 4 days and 8 capsules per day were given in 2 daily doses in the following 3 days. After a washout and baseline period of 1 week each, patients crossed over to the second 7-day treatment period.

**Main Outcome Measures**
Visual analog scale (VAS) and verbal rating scale scores for pain; vital sign, hematologic and blood chemistry, and electrocardiogram measurements; scores on the Trail-Making Test and the Addiction Research Center Inventory–Marijuana scale; and adverse effects.

**Results**
The mean differences over time for the VAS values in the CT-3–placebo sequence measured 3 hours after intake of study drug differed significantly from those in the placebo–CT-3 sequence (mean [SD], −11.54 [14.16] vs 9.86 [21.43]; P=.02). Eight hours after intake of the drug, the pain scale differences between groups were less marked. No dose response was observed. Adverse effects, mainly transient dry mouth and tiredness, were reported significantly more often during CT-3 treatment (mean [SD] difference, −0.67 [0.50] for CT-3–placebo sequence vs 0.10 [0.74] for placebo–CT-3 sequence; P=.02). There were no significant differences with respect to vital signs, blood tests, electrocardiogram, Trail-Making Test, and Addiction Research Center Inventory–Marijuana scale. No carryover or period effects were observed except on the Trail-Making Test.

**Conclusions**
In this preliminary study, CT-3 was effective in reducing chronic neuropathic pain compared with placebo. No major adverse effects were observed.
without psychoactive properties. Although the exact neurobiological mechanism of action is still unclear, some evidence exists that apart from the known cannabinoid receptors (CB1 and CB2), 1 or more undiscovered cannabinoid receptors are involved in mediating the analgesic and anti-inflammatory effects of CT-3. In addition, other studies suggest possible postreceptor mechanisms, including inhibition of eicosanoid synthesis and down-regulation of cyclooxygenase. Recent data suggest that the peroxisome proliferator-activated receptor γ (PPARγ) may serve as an intracellular receptor for CT-3. The activation of PPARγ is directly linked to anti-inflammatory and antitumor processes.

The aim of this preliminary study was to examine the analgesic efficacy and safety of CT-3 in chronic neuropathic pain.

METHODS

Patients

Newspaper advertisement led to 196 telephone contacts. Only 48 of the contacted individuals appeared to have neuropathic pain and were invited to an interview. Among these, 24 had both neuropathic and somatic pain and were therefore excluded. Three patients were denied participation because of the long distance from their homes to the study site. Inclusion criteria were pain for at least 6 months, stable levels of pain medications for at least 2 months, age 18 to 65 years, and consent to participate in the study and follow study procedures. Concomitant pain-relieving medications allowed were antipyretic and opioid analgesics, flurbiprofen, anticonvulsants, and antidepressants. Not allowed were N-methyl-D-aspartate receptor antagonists and cannabinoids. Other specific exclusion criteria were severe organic or psychiatric disease, pregnancy or attempting to conceive, lactation, use of any investigational drug within 30 days prior to first dose of study drug, and non–German speaking. The selected 21 patients (8 women and 13 men) aged 29 to 65 years (mean, 51 years) had a clinical presentation and examination consistent with chronic neuropathic pain with hyperalgesia (n=21) and allodynia (n=7).

Diagnoses in the study group included neuropathic pain of the left arm (n=5) and right arm (n=1) due to traumatic cervicobrachial plexus lesions, mainly at C5 to C8; neuropathic facial pain (n=3) due to traumatic lesions of the left maxillary nerve, left trigeminal nerve, and mental nerve bilaterally; neuropathic pain behind the left ear (n=1) due to traumatic lesion of the left great auricular nerve; neuropathic pain of the left forearm and hand (n=1) due to traumatic lesion of the left radial nerve; neuropathic pain in the left leg (n=3) and right leg (n=1) due to lumbar disk protrusion or intraspinal scar tissue after lumbar disk surgery, mainly at L5/S1; neuropathic pain in one or both of the legs (n=3) due to traumatic spinal cord lesions at L1; neuropathic pain of the sole of the left foot due to compression of the tibial nerve (tarsal tunnel syndrome) (n=1); neuropathic whole-body pain below the shoulders due to tethered cord syndrome after surgical removal of an intrathecally ependymoma at C4 to T1 (n=1); and neuropathic left facial pain of unknown cause (n=1) of unknown cause. The study protocol was approved by the Hannover Medical School Institutional review board, Hannover, Germany, and the German Federal Institute for Drugs and Medical Devices, and written informed consent was obtained from all patients.

Study Design and Assessment

This randomized, double-blind, placebo-controlled crossover study was conducted from May-September 2002 and lasted 5 weeks (FIGURE 1). Weeks 1 and 4 were baseline weeks, weeks 2 and 5 were intervention weeks, and week 3 was a washout period. Patients were randomized either to CT-3 or to placebo. During the first intervention week, 2 daily doses were given (four 10-mg CT-3 capsules per day) during the first 4 days and 8 capsules per day in 2 daily doses during the following 3 days; placebo was administered in the same amounts and with the same appearance of capsules. After a washout period of 1 week, the patients crossed over to the alternate group for another 7-day treatment period. For measurement of pain, during each baseline week and each intervention week, patients completed a visual analog scale (VAS) and a verbal rating scale (VRS) twice per day (11 AM and 4 PM, 3 and 8 hours after the morning dose, respectively) for 1 week and recorded the values in a patient diary.

The VAS consisted of a 100-mm horizontal line with 2 end points labeled as 0 (no pain) and 100 (worst pain ever). The VRS consisted of a series of verbal pain descriptors ordered from least to most intense (none=0, weak=1, moderate=2, severe=3, and excruciating=4).

The CT-3 was produced by Cresspharm, Le Haillan, France. The drug substance was mixed with an appropriate amount of lactose and filled into No. 2 hard gelatin capsules at 10 mg each. Placebo capsules were identical in all respects except for the absence of CT-3. Randomization, labeling, and packag-
Subjective drug effects were determined using the 12-item ARCI-M scale, which derives from a 53-item version of the ARCI® plus 4 items specific to marijuana. These 4 items are “I have difficulty in remembering,” “My mouth feels very dry,” “I notice that my heart is beating faster,” and “My thoughts seem to come and go.” The items are answered as true or false, and each true response is scored as 1 point.

Response was assessed with a pain diary in which the patients completed theVAS and VRS at 11 AM and 4 PM at each day, 3 and 8 hours after the morning intake of the capsules, respectively. In addition, spontaneous adverse events were collected in the diaries. On the first and last days of the treatment week, the TMT and ARCI-M scale were administered along with an electrocardiogram. On the first, fifth, and last days of the treatment week, hematologic and blood chemistry measurements were taken. Vital signs were measured daily. All measurements were performed at least 2 hours after intake of the morning dose of the study drug. Furthermore, at each appointment, compliance was assessed by collection of the study medication bottles. Patients were not asked to guess which treatment they had received during each period; some patients commented on this point but no responses were made regarding these comments.

**Statistical Analysis**

We assumed that there would be no carryover effect after the washout period of 1 week (week 3). The α level was .05 with a power of 90%. Using a 2-sided test with a 2-period crossover design resulted in the need to enroll a total of 21 patients.

Results are presented as means (SDs). Demographic data, duration of pain, and pain intensity were analyzed with the unpaired t test; sex, type of neuropathic pain, presence of allodynia, and regular use of concomitant pain medication were measured as frequency data. Categorical data were analyzed with the Fisher exact test. Pain scores, the TMT, the ARCI-M scale, and vital signs were computed for treatment effects, period effects, and carryover effects by the method reported by Hills and Armitage for 2-period crossover clinical trials. These quantitative data were analyzed using the unpaired t test to evaluate between-group differences in the 2 sequence groups. For the analysis of pain-reducing effects of the intervention period, the differences between each intervention week’s results and the corresponding baseline week results (week 2 – week 1 and week 5 – week 4) were computed. For the analysis of the difference over time, the difference (week 2 – week 1) – (week 5 – week 4) was computed. Statistical significance was determined as P < .05. Analyses were conducted using SPSS, version 11.0 (SPSS Inc, Chicago, Ill).

**RESULTS**

**Patient Characteristics and Disposition**

Of the 21 patients, 10 were randomly assigned to receive CT-3 first then placebo, and 11 were assigned to receive placebo first, then CT-3 (Figure 1). The 2 groups were well balanced with respect to age, sex, duration of pain, type of neuropathic pain, and regular use of concomitant analgesics (opioids, anticonvulsants, antidepressants, antipyretic analgesics), and mainly central-acting compounds (diazepam and zolpidem) (Table). In 10 patients, the following pain medications and dosages were in regular use: 1 patient each took metamizol, 1000 mg every 6 hours; metamizol, 750 mg every 4 hours; controlled-release morphine, 90 mg, and diazepam, 10 mg, every 24 hours; controlled-release formulation of oxycodone, 100 mg every 6 hours; zolpidem, 10 mg every 4 hours (abusingly); doxepin, 25 mg in the evening, imipramine, 20 mg twice per day, and sublingual buprenorphine every 6 hours; controlled-release tramadol, 100 mg every 8 hours; celexcoxib and citalopram once per day, flupirtine, 100 mg every 6 hours, and gabapentin, 100 mg every 8 hours; controlled-release tramadol, 100 mg every 12 hours; and controlled-release tilidine/naloxone, 100/8 mg in the morning, amitriptyline, 50 mg in the evening, and gabapentin, 300 mg every 8 hours.

At both baseline weeks, mean (SD) pain levels on the VAS were between...
...56.00 (20.93) and 68.07 (14.25) for the entire group. With the exception of the 4 PM VAS assessment in week 1, both sequence groups differed significantly in their baseline VAS scores (11 AM in week 1, P = .03; 11 AM in week 4, P = .002; and 4 PM in week 4, P = .03) (Table 1).

Two patients dropped out on the second day of the first intervention week. Therefore, their small amount of data was not considered for further analysis or imputation methods, which led to a modified intention-to-treat analysis. One of these patients, a placebo patient with no history of cardiovascular disease, experienced elevated blood pressure (214/105 mm Hg) and tachycardia (122/min). The patient was referred to a cardiologist. One patient treated with CT-3 experienced severe drowsiness, which interfered with his work. This patient was also taking a controlled-release preparation of oxycode, 100 mg every 6 hours.

### Pain Measurements

Morning Measurements

Morning measurements (3 hours after intake of the study drug) of the CT-3 intervention weeks (weeks 2 and 3) showed significant reduction in pain scores and a strong tendency toward significant pain reduction as measured by mean (SD) VAS and VRS differences over time ([week 2 − week 1] − [week 5 − week 4]), respectively. For the CT-3–placebo sequence, the difference in VAS scores for week 2 − week 1 was −13.07 (13.76), for week 5 − week 4 was −1.52 (12.98), and the difference over time was −11.54 (14.16). For the placebo–CT-3 sequence, the difference in VAS scores for week 2 − week 1 was −3.14 (13.11), for week 5 − week 4 was −13.00 (22.14), and the difference over time was 9.86 (21.43); P = .02 by independent t test (Figure 2A). For the CT-3–placebo sequence, the difference in VRS scores for week 2 − week 1 was −0.36 (0.47), for week 5 − week 4 was −0.11 (0.40), and the difference over time was −0.25 (0.49). For the placebo–CT-3 sequence, the difference in VRS scores for week 2 − week 1 was −0.19 (0.55), for week 5 − week 4 was −0.61 (1.01), and the difference over time was 0.42 (1.05); P = .10 by independent t test (Figure 2B).

The afternoon results (8 hours after morning intake of the study drug) showed less marked effects. For the CT-3–placebo sequence, the difference in VAS scores for week 2 − week 1 was −15.56 (23.38), for week 5 − week 4 was −5.91 (14.82), and the difference over time was −9.65 (29.15). For the placebo–CT-3 sequence, the difference in VAS scores for week 2 − week 1 was −8.26 (11.39), for week 5 − week 4 was −12.39 (14.48), and for the difference over time was 4.13 (10.43); P = .21 by independent t test (Figure 2A). For the CT-3–placebo sequence, the difference in VRS scores for week 2 − week 1 was −0.57 (0.95), for week 5 − week 4 was −0.25...
(0.55), and the difference over time was
−0.32 (1.13). For the placebo–CT-3 se-
cquence, the difference in VRS scores for
week 2 – week 1 was −0.29 (0.38), for
week 5 – week 4 was −0.62 (0.74), and
the difference over time was 0.33 (0.66); 

\( P=.14 \) by independent \( t \) test (Figure 2B).

The effect size for CT-3 was some-
what greater in the CT-3–placebo se-
cquence, with less pain intensity at base-
line (Table 1) than in the placebo–
CT-3 sequence. The VAS and VRS
reductions in the CT-3–placebo se-
cquence at 11 AM were 28.84% and
18.89% and at 4 PM were 26.75% and
23.76%, respectively. In contrast, the
VAS and VRS reductions in the pla-
cebo–CT-3 sequence at 11 AM were
18.40% and 21.49% and at 4 PM were
16.59% and 20.13%, respectively.

All patients used the opportunity to
increase the dosage on day 5 of each in-
tervention week, but no significant dose
response or increase in adverse events
was observed. No carryover or period
effects were observed.

**Adverse Events**

Reported adverse events were mainly
tiredness and dry mouth but also in-
cluded limited power of concentration,
dizziness, sweating, and more pain.
These adverse events were reported sig-
nificantly more often when CT-3 was ad-
mistered (mean [SD] difference over
time, −0.67 [0.50] for CT-3–placebo
sequence vs 0.10 [0.74] for placebo–
CT-3 sequence; \( P=.02 \) by independent
\( t \) test). In the CT-3–placebo sequence,
during the CT-3 period, 6 of 9 patients
reported such adverse events vs 0 of 9
in the placebo period. In the placebo–
CT-3 sequence, 6 of 10 reported ad-
verse events in the CT-3 period vs 5 of
10 in the placebo period. Neither the
TMT nor the ARCI-M scale scores
showed significant differences over time
between the 2 treatment groups. The mean
(SD) difference over time for the
TMT score was 35.89 (112.80) seconds
in the CT-3–placebo sequence and was
3.15 (63.45) seconds in the placebo–
CT-3 sequence. On the ARCI-M, the
mean (SD) difference over time for the
number of items answered as true was
−0.67 (3.61) in the CT-3–placebo se-
cquence and was 0.22 (2.59) in the pla-
cebo–CT-3 sequence. However, there
was a carryover effect observed with the
TMT (\( P=.03 \)). No significant differ-
ences were found with respect to changes
in vital signs, weight, temperature, elec-
etrocardiographic findings, or hemat-
ologic and blood chemistry studies.

**COMMENT**

**Neuropathic Pain**

Understanding of the etiology and
pathophysiology of neuropathic pain has
increased over the past few years, par-
ticularly on a molecular and genetic
level. Activation of intracellular signal
transduction cascades results in changes
of receptor and ionic channel function,
which may remain active following ini-
tial trauma (long-term potentiation).\(^9\)
There is still much to be understood be-
tween the etiological findings and the
therapeutic possibilities.

Neuropathic pain cannot be totally
eliminated by means of preventive meas-
ures, and there is no completely effec-
tive medication available with an ac-
ceptable therapeutic ratio of efficacy to
safety. Apart from inhibiting sodium-
ion channels (by use of anticonvul-
sants or local anesthetics) and assist-
ing endogenous noradrenergic and
serotonergic mechanisms (by use of antidepressants), an increasing
number of N-methyl-D-aspartate receptor
antagonists have been introduced in the
past few years. Many of these have pro-
duced favorable therapeutic results.\(^10\)
Nevertheless, their use is restricted by
a poor adverse effect profile; thus, there
is a need for effective alternatives with
acceptable adverse effect profiles.

**Cannabinoids for Chronic Pain**

Preclinical studies have shown that
cannabinoids reduce the hyperalgesia and
allodynia associated with formalin, cap-
saicin, carrageenan, nerve injury, and
visceral persistent pain\(^11\); therefore, ex-
genous cannabis or cannabinoids may
work as an analgesic in poorly con-
trolled neuropathic pain. In addition,
humans have cannabinoid receptors in the
central and peripheral nervous sys-
tem,\(^12\) although the functions of these
receptors and their endogenous li-
gands remain unclear.

Although a large number of case re-
ports and letters suggest the benefits of
cannabis or cannabinoids in chronic pain
and other conditions, there is little re-
search-based evidence.\(^13\) Oral THC, 5 to
20 mg, was found to have an analgesic
effect compared with placebo in 10 pa-
tients with pain related to advanced can-
cer.\(^14\) In this study, a dose-response re-
lationship was shown for analgesia and
adverse effects. In a further study by
the same research group, THC, 10 mg, was
found to be equipotent to codeine, 60
mg, and THC, 20 mg, was equipotent to
codeine, 120 mg, but the higher dose
was associated with unacceptable ad-
verse effects.\(^15\) In a patient with neuro-
pathic pain and spasticity secondary to
a spinal cord ependymoma, THC, 5 mg,
and codeine, 50 mg, were equianalge-
sic, and both were superior to placebo.
Only THC, however, had a beneficial
effect on spasticity.\(^16\)

Tetrahydrocannabinol has psycho-
logical adverse effects including psy-
chomotor and cognitive impairment,
anxiety and panic attacks, and acute
psychosis and paranoia\(^17\) and adverse
physical effects including dry mouth,
blurred vision, palpitations, tachycar-
dia, and postural hypotension\(^18\) in doses
as low as 10 to 20 mg.

**Pharmacokinetics**

CT-3, a synthetic analog of THC-11-oc-
ic acid, has been shown in animal tests to
have potent anti-inflammatory, analge-
sic, and antiallodynic effects without psy-
choactive properties.\(^2\) The following find-
ings recently have been corroborated:
The absence of psychoactive properties
was confirmed in 24 human volunteers
with a dose of up to 10 mg of CT-3 (S.B.,
unpublished data, 2001). After a single
oral administration of CT-3 in 6 human
volunteers, the time to highest plasma
concentration (\( t_{\text{max}} \)) was reached in most
participants 1 or 2 hours after absorp-
tion from the empty gastrointestinal tract,
but some participants had a delayed \( t_{\text{max}} \)
of 4 to 5 hours. Furthermore, plasma

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concentrations of CT-3 demonstrated a strong linear relationship to dose. The peak plasma concentrations of CT-3 increased in ratios of 3.7, 6.2, and 12.6 for CT-3 doses of 3, 6, and 10 mg compared with 1 mg. Similarly, the extrapolated area under the curve (AU_{0-8}) of CT-3 increased in ratios 3.6, 5.5, and 11.0, respectively. Moreover, in rats and dogs, concentration of CT-3 in plasma reached peak levels 1.5 to 6 hours after dosing and declined thereafter with apparent half-lives of 4 to 13 hours, although longer half-lives may have occurred in some female dogs at high doses.

Our investigation showed that CT-3, given in daily doses of 40 and 80 mg, is more effective than placebo for neuropathic pain, with greater pain-reducing effects at 3 hours after intake than at 8 hours. These findings may confirm the pharmacokinetic data regarding CT-3 known in humans and animals, with mild clinical effects observed in the first 6 hours after intake of the drug. The observation of prolonged effects in animal studies could not be confirmed statistically in this study; nevertheless, even 8 hours after intake of the drug, there was a tendency toward more pain reduction during the CT-3 intervention. Considering the small sample size, this result may have more weight than the statistical analysis indicates. Furthermore, the amount of pain reduction by the study drug was generally more marked in patients with lower baseline pain levels. This finding may be an indication of a limitation of the pain-reducing efficacy of the compound and a general observation that mild pain is easier to reduce than severe pain. Elevation of the dose increased neither pain reduction nor adverse events, which may be a strong argument for 20 mg as a single dose for this compound.

**Adverse Events**

CT-3 appeared to be free of psychoactive properties as measured by the TMT and the ARCI-M scale, though the assessment of the TMT was restricted by the observed carryover effect. The TMT is often used for screening for cognitive impairment in marijuana users. We restricted the use of the TMT to part B because only part B is a general indicator for brain dysfunction. Its cognitive demands include visual scanning, visual-motor coordination, and visual-spatial ability adequate enough to understand on an ongoing basis the alternating pattern of numbers and letters. In addition, in terms of construct validity, there are several factors that make part B more difficult. The ARCI-M scale was used as an outcome measure for subjective effects because in previous studies of THC and marijuana, increases in the ARCI-M scale were observed together with prototypic subjective experiences with marijuana use.

In our study, tiredness was the main adverse psychological event and dry mouth was the main adverse physical effect; major physical adverse events were not observed. Only 1 CT-3-related dropout occurred (because of severe drowsiness) when CT-3 was used in conjunction with a high dosage of oxytocin (400 mg/d).

**CONCLUSION**

Because this preliminary study showed the effectiveness of CT-3 in neuropathic pain and did not find clinically relevant adverse events, and because in animal studies no signs of strong dependency after withdrawal of the drug have been found, further clinical studies with CT-3 are warranted. Future studies with this agent should be conducted over weeks or months and should consider a shorter dosing interval, such as 6 to 8 hours.

**Author Contributions:** Dr Karst, as principal investigator, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Karst, Salim, Conrad, Schneider. Acquisition of data: Karst, Salim, Burstein, Conrad. Analysis and interpretation of data: Karst, Conrad, Hoy, Schneider. Drafting of the manuscript: Karst, Salim, Hoy. Critical revision of the manuscript for important intellectual content: Karst, Salim, Burstein, Hoy, Schneider. Statistical expertise: Karst, Conrad, Hoy. Obtained funding: Karst, Schneider. Administrative, technical, or material support: Karst, Salim, Conrad. Study supervision: Karst, Conrad, Schneider. Funding/Support: This study was supported by a research grant from Atlantic Technology Ventures Inc (which paid for the CT-3 used in this study) and Invivus Pharmaceuticals Inc.

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