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Pain measurements and side effect profile of the novel cannabinoid ajulemic acid

Kahlid Salim [a], Udo Schneider [b], Sumner Burstein [c], Ludwig Hoy [d], Matthias Karst [a,*]

[a] Department of Anesthesiology, Pain Clinic, Hannover Medical School, D-30623 Hannover, Germany
[b] Department of Clinical Psychiatry and Psychotherapy, Hannover Medical School, Hannover, Germany
[c] Department of Biochemistry and Molecular Pharmacology, University of Massachusetts Medical School, USA
[d] Department of Biometrics, Hannover Medical School, Hannover, Germany

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Abstract

Preclinical findings on ajulemic acid (AJA) showed analgesic and anti-allodynic effects without psychoactive properties making it an appealing substance for the treatment of pain. A recently published randomized double-blind crossover clinical trial described the pain-reducing effects and side effect profile of AJA on 21 patients with chronic neuropathic pain. In this report from this same sample the effects of AJA on the mechanical hypersensitivity, on pain, and on psychological and physical performance were further characterized.

During a 5-week study period, patients were divided into two 7-day treatment groups receiving either AJA or placebo capsules first, respectively. All patients received 40 and 80 mg of AJA or placebo daily in each treatment period. Pain measurements included the determination of mechanical hypersensitivity using the von Frey hair method as well as the visual analog scale (VAS), for which the number needed to treat (NNT) was calculated. The side effect profile of the compound was evaluated using psychotropic and physical measurements as well as obtaining reports on possible subjective side effects.

The results showed no significant reduction in mechanical hypersensitivity ($p = 0.052$), although a tendency towards pain reduction could be seen. The VAS score showed significant pain reduction ($p = 0.021$) and NNT values for 30% pain relief were 2.14 for the first treatment group and 5.29 for the second treatment group. No significant findings were observed regarding psychotropic or physical measurements. Reported subjective side effects were mainly dry mouth, tiredness and dizziness and did not increase with dose elevation.

Overall, these study findings indicate that AJA shows pain-reducing effects on patients with chronic neuropathic pain without clinically relevant psychotropic or physical side effects.

Keywords: Ajulemic acid (AJA); CT-3; Cannabinoid; Visual analog scale; von Frey hair; Trail-Making Test (TMT); Addiction Research Center Inventory-Marijuana (ARCI-M); Neuropathic pain

1. Introduction

Chronic neuropathic pain presents a clinical field of high therapeutic need largely due both to the relatively large number of patients (1% of the western world-population) and to unmet pharmaceutical goals (Bennett, 1998; Attal, 2001). Current treatment options for this condition most often involve tricyclic antidepressants and anti-convulsants, with only 34% of patients with neuropathic pain achieving significant pain relief (Hempenstall and Rice, 2002; Collins et al., 2000). The introduction of *N*-methyl-D-aspartate (NMDA) receptor antagonist

* Corresponding author. Tel.: +49 511 5323108; fax: +49 511 5328109.
E-mail address: karst.matthias@mh-hannover.de (M. Karst).

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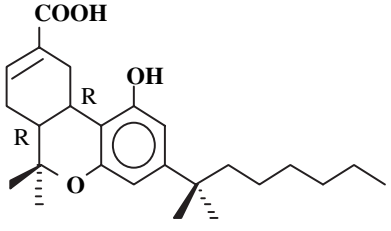
shows promising therapeutic options, even though their clinical use seems to be currently restricted by a significant adverse effect profile (Weber, 1998).

A possible therapeutic solution to this need might be a synthetically modified compound derivative of a metabolite of delta-9-tetrahydrocannabinol (THC), a major constituent of the *Cannabis sativa* plant. Synthetic modification of this THC metabolite THC-11-oic acid through replacement of the *n*-pentyl side chain with a dimethylheptyl group leads to the compound 1,1-dimethylheptyl-Δ^8-THC-11-oic acid, named ajulemic acid (AJA, also called CT-3 or IP-751) (Fig. 1) (Burstein et al., 1992).

In preclinical studies by Burstein et al. (1992, 1998) AJA showed high analgesic potency comparable to morphine, as well as anti-allodynic and anti-inflammatory effects. AJA appears to have no detectable THC like psychoactive properties (such as anxiety, panic attacks, acute psychosis, paranoia, psychomotor and cognitive impairment) and is not ulcerogenic at therapeutic doses nor does it induce tolerance or cause mutagenesis (Burstein, 2000; Dajani et al., 1999). Mechanisms of action responsible for these effects are still not fully understood. Some evidence exists that AJA does not bind strongly to the well-known cannabinoid receptors (CB1 and CB2), and that other yet-to-be discovered receptors seem to be responsible for its analgesic effects. Other studies suggest selective inhibition of eicosanoid synthesis and modulation of cyclooxygenase 2 (Burstein et al., 2004). In addition, recent data indicate that the peroxisome-proliferator activated receptor γ (PPAR γ) may serve as an intracellular receptor, in particular, for the anti-inflammatory actions of AJA (Liu et al., 2003).

Neuropathic pain after nerve injury is thought to lead to a reorganization of synaptic connections made by low-threshold mechanoreceptors in the spinal cord. Under these circumstances, light pressure activation of low-threshold mechanoreceptors can lead to pain because of altered synaptic connectivity in the spinal cord (Lewin and Moshourab, 2004). Quantitative sensory testing helps to detect and determine pain thresholds by applying stimuli to the skin in an ascending and descending order of magnitude. Mechanical sensitivity for tactile stimuli is often measured using von Frey hairs. This method is particularly appropriate to quantify mechanical allodynia and the effects of treatments on allodynia and hyperalgesia (Cruccu et al., 2004). However, the analysis of perception in response to external stimuli of controlled intensity has never been used to make a differential diagnosis between neuropathic and non-neuropathic pains (Cruccu et al., 2004).

In the first report of this study it could be demonstrated that AJA had significant pain-reducing effects as measured by the visual analog scale (VAS) on 21 patients with chronic neuropathic pain (Karst et al., 2003). The aim of this article was to analyze the secondary outcomes of that study such as mechanical hypersensitivity (allodynia and hyperalgesia) as well as psychotropic and physical effects under AJA treatment. In addition, the number needed to treat (NNT) for pain reduction was calculated.



AJULEMIC ACID (CT-3)

Fig. 1. Structure of ajulemic acid (AJA). Also known as CT-3 and IP-751.

2. Methods

2.1. Study population

The study, approved by the local institutional review board and the German Federal Institute for Drugs and Medical Devices, was conducted in the Pain Clinic at Hannover Medical School, Hannover, Germany from May to September 2002.

The required sample size to achieve a 90% power for the expected differences between mean values was calculated as 21 in total.

Regional newspaper announcements led to 196 telephone contacts and interviews, from which 21 patients were chosen to participate in the study. Inclusion criteria for patient selection were: age 18–65 years, neuropathic pain for at least six months, stable levels of pain medications for at least 2 months and consent to participate and follow the study procedures. Previously prescribed pain-relieving medications (antipyretics (NSAIDs), opioid analgesics, anti-convulsants, tricyclic antidepressants) could be used concomitantly and had to remain unchanged throughout the study. Type of medications taken concomitantly by the study subjects was: opioids, anti-convulsants, antidepressants, NSAIDs, as well as centrally acting compounds (diazepam and zolpidem). Exclusion criteria were: severe organic or psychiatric disease, pregnancy, lactation or women attempting to conceive, use of any investigational drug within 30 days prior to first dose of study drug, and current cannabis use (patients were questioned for previous or current cannabis use, but a cannabis urine test was not performed).

All 21 patients fulfilling the selection criteria (8 women and 13 men, aged 29–65 years) had clinical symptoms consistent with chronic neuropathic pain, including hyperalgesia ($n = 21$) and allodynia ($n = 7$). Clinical diagnoses of the study group differed in their causes of neuropathy but all were caused by mechanical trauma (Table 1).

2.2. Study design

This was a randomized, double-blind, placebo-controlled crossover phase II clinical trial for a total time of five weeks (study days 1–35). Patients were randomized to receive AJA (verum) in the first treatment period (verum–placebo group) or to receive placebo in the first treatment period (placebo–verum group). In the second treatment period each group received the alternative intervention (Table 2). Verum or matching placebo capsules were administered twice daily for 7 days at 8 AM and 8 PM for each treatment period, i.e. week 2 (days 8–14) and week 5 (days 29–35), respectively. The daily dose for the first 4 days was 40 mg (20 mg twice daily) and during the last 3 days a doubled dose of 80 mg (40 mg twice daily) was given. In between each treatment period was a washout-phase of 1 week (week 3; days 15–21), after which patients crossed-over to the alternate group of either placebo or active-drug. Each patient attended the clinic during baseline (day 1 and day 22), and on days 8, 12 and 14 (week 2) and days 29, 33 and 35 (week 5) of each treatment period and for one final follow-up evaluation. For measurement of pain, patients were given a pain-diary (visual analog scale and verbal rating scale) to maintain during the study period.

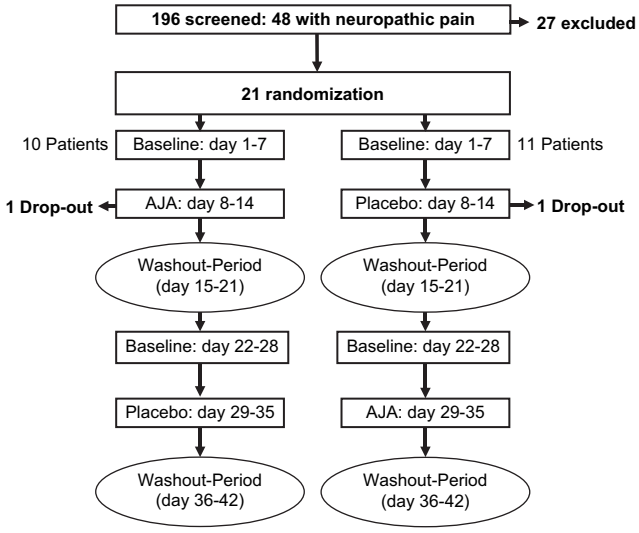
AJA was produced, filled in capsules and labeled and packaged by Creapharm, Le Haillan, France, who also provided the computer-based randomization for the study medication under blinded conditions. All study bottles were labeled from 1 to 21 and patients were allotted randomization numbers on the day 1 visit. Study investigators were also blinded to the randomization method.

Table 1
Characteristics of 21 patients who participated in the study, presented as the number or mean (range) ± standard deviation (SD)

Characteristics	Value
Gender (male/female)	13/8
Age (years)	50.86 (29–65)
Number of patients with concomitant use of analgesics (yes/no)	10/11
VAS[a] week 1, 11 AM	56.00 ± 20.93
VAS[a] week 1, 4 PM	64.63 ± 17.62
VAS[a] week 4, 11 AM	60.00 ± 17.63
VAS[a] week 4, 4 PM	68.07 ± 14.25
von Frey hair values (g) week 1, 11 AM	2.52 ± 3.43
von Frey hair values (g) week 4, 11 AM	3.69 ± 5.64
Duration of pain (years)	11.48 ± 7.15
Clinical diagnosis	**Number of patients**
Peripheral neuropathic pain	
Cervicobrachial plexus lesions	6
Neuropathic facial pain due to traumatic nerve lesions	3
Neuropathic facial pain of unknown cause	1
Auricular nerve injury	1
Left forearm and hand: radial nerve injury	1
Tibial nerve compression (tarsal tunnel syndrome)	1
Leg pain due to lumbar disc injury (L5/S1)	4
Central neuropathic pain	
Leg pain due to traumatic spinal cord lesion (L1)	3
Tethered cord syndrome after surgical removal of intrathecal ependymoma (C4 to T1)	1

Week 1 and week 4: baseline weeks.
[a] Range 0–100.

Table 2
Flow of participants and scheme of the treatment and assessment plan



2.3. Assessment

Pain measurements were performed using the visual analog scale (VAS, 0–100 mm; 0, no pain; 100, worst pain ever) and a verbal rating scale (VRS; 0, none; 4, excruciating) as well as testing of mechanical hypersensitivity (i.e. hypersensitivity restricted to the area of the injured nerve). VAS and VRS were completed by the patients as part of their pain-diary beginning on day 1 twice daily (3 and 8 h after the morning dose, respectively) and ending on day 14, last day of the treatment period. Mechanical hypersensitivity was

determined using graded monofilaments (von Frey Hairs (0.008–300 g; Stoelting Co., Wood Dale, IL)) during the baseline weeks at days 1 and 22 and 3 h after the morning drug administration during the treatment periods at days 8 and 14, as well as on days 29 and 35, respectively. For consistent positioning of the von Frey hairs during the whole treatment phase, patients were asked on day 1 of their first visit to pinpoint a spot of heightened pain sensibility within their area of neuropathy that is usually not changing its location. This area was marked with a pen for the next clinical appointment. Applying different monofilaments of varying pressure to the skin determined the baseline value in gram force for the mechanical hypersensitivity test (Pedersen et al., 1996).

Psychometric tests, involving the Trail-Making Test (TMT) and the Addiction Research Center Inventory-Marijuana (ARCI-M) were performed on baseline (days 1 and 22) and days 8 and 14, as well as days 29 and 35, at least 2 h after drug administration during treatment periods. Part B of the TMT was used to determine impairment of cognition, consisting of a 1-page worksheet with scattered numbers and letters. Patients were asked to connect consecutively between numbers and letters, without lifting the pencil. The test was scored by time to completion and number of errors (Bradford, 1992). Subjective drug effects were determined using the 12-item ARCI-M scale, which is derived from a 53-item version of the ARCI plus four items specific to marijuana (Martin et al., 1971; Chait et al., 1985). These four 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.

Physical parameters, including blood pressure, temperature, pulse rate, breathing frequency and weight were measured on baseline (days 1 and 22) and from the beginning of the treatment period by day 8 until day 14, and from day 29 until day 35, daily. On days when no clinical visits were scheduled, patients were instructed to measure their vital parameters at home and report them on their next scheduled appointment. Electrocardiogram, hematological- and blood-chemistry tests were performed on each clinical visit. Additionally, patients were instructed to record in their pain-diary any adverse events and changes in regular medication during the periods in between hospital visits.

2.4. Statistical analysis

Mechanical hypersensitivity and pain scores, including VAS, VRS as well as the TMT, the ARCI-M scale and vital signs were computed for treatment effects, period effects and carryover effects. For this, the method reported by Hills and Armitage (1979) for a two-period crossover clinical trial was used. Quantitative data were analyzed using the unpaired t test to evaluate between-group differences in the two-sequence groups. For the analysis of changes in mechanical hypersensitivity and VAS scores of the treatment period the differences between each treatment week's results and the corresponding baseline week's results (week 2 – week 1 and week 5 – week 4) were computed. For the analysis of the differences over time, the difference (week 2 – week 1) – (week 5 – week 4) was computed. The α level was set at 0.05 with a power of 90%. Statistical significance was determined as $p < 0.05$. The number needed to treat (NNT) was calculated by the formula: 1/(the proportion of patients successfully treated with active treatment minus the proportion of patients successfully treated with placebo). Successful treatment was set at 30% pain relief assessed by the VAS.

3. Results

From 21 patients enrolled, 10 were randomized to receive verum (AJA) first then placebo (verum–placebo group), the other 11 received placebo first then verum (placebo–verum group). Characteristics of the 21 patients are shown in Table 1. Both groups were well balanced with respect to age, gender, duration of pain, type of neuropathic pain and use of concomitant medication, but both sequence groups differed significantly in their baseline VAS scores (data shown in Karst et al., 2003). Two patients dropped out on the second day of the first treatment week. Their small amount of data was not considered for further analysis, which led to a modified intention-to-treat analysis. One patient under placebo experienced elevated blood pressure (214/105 mmHg) and tachycardia (122/min) and was referred to a cardiologist. One other patient treated with AJA experienced severe drowsiness, which interfered with his work. This patient was also taking a controlled-release preparation of oxycodone, 100 mg every 6 h.

Graded monofilaments (von Frey hair) values, which determine mechanical hypersensitivity, were converted into gram force in 18 patients (measurement was not possible for one patient due to numbness of the neuropathic extremity). Mean baseline levels were lower in the verum–placebo group (1.17, SD: 1.97; $n = 8$) than in the placebo–verum group (3.60, SD: 4.04; $n = 10$; difference n.s.). Differences over time in the verum–placebo group were 0.69 (SD: 3.32) and in the placebo–verum group −4.06 (SD: 5.52). Mechanical testing by graded monofilaments did not show significant levels of reduction in sensitivity ($p = 0.052$), although a tendency towards decreased sensitivity could be observed in the verum–placebo group (Fig. 2). No carryover or period effects were observed.

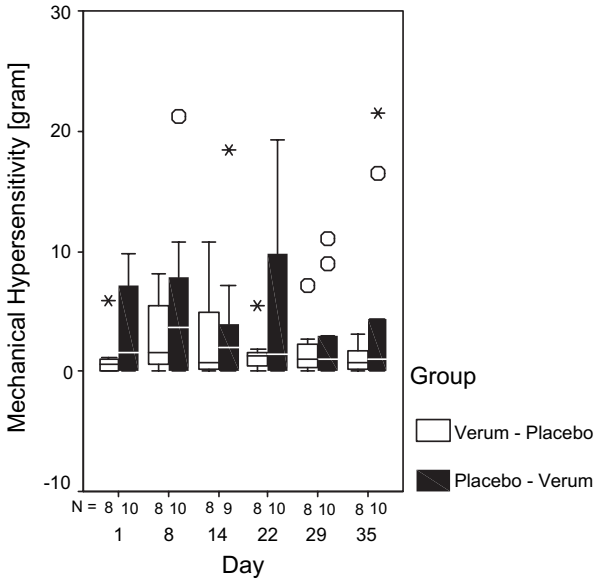


Fig. 2. Mechanical hypersensitivity testing on the study group. Mechanical hypersensitivity scores as measured by the von Frey hair method were obtained from the study group presenting typical neuropathic symptoms of hyperalgesia and allodynia. The verum–placebo group received verum (AJA) in the first treatment period (days 8–14) and placebo in the second treatment period (days 29–35). The placebo–verum group received placebo in the first treatment period and verum (AJA) in the second treatment period. Days 1 and 22 were each baseline days. The figure indicates a decrease in sensitivity by day 8 as shown by an elevation of the median. However, this tendency towards pain reduction, seen by the verum–placebo group did not show statistical significance ($p = 0.052$). Medians (black bars), interquartile ranges (boxes), whole ranges (t-hairs), extreme values (circles) and outliers (stars) are indicated.

The observation that the primary end point VAS decreased significantly 3 h after administration of AJA compared with placebo ($p = 0.021$) has been described in detail previously (Karst et al., 2003). In the first intervention week the number of patients on AJA who had at least 30% (50%) reduction in pain was 6 from 9 (1 from 9) compared with 2 from 10 (0 from 10) on placebo with same response. In the second intervention week the number of patients on AJA who had at least 30% (50%) reduction in pain was 3 from 10 (1 from 10) compared with 1 from 9 (0 from 9) on placebo with same response. Based on the number of patients with least 30% pain relief 3 h after intake of the study medication the number needed to treat (NNT: 1/(the proportion of patients successfully treated (30% pain relief) with active treatment minus the proportion of patients successfully treated with placebo)) was 2.14 for the first period and 5.29 for the second period (Table 3). Eight hours after the morning dose of the study medication there was still a tendency towards more VAS reduction with verum but the results failed the statistical significance (data shown in Karst et al., 2003). The VRS values reached no statistical significance but showed, in addition, more reduction during the active

Table 3
Number needed to treat (NNT) for 30% pain relief as determined by the visual analog scale (VAS) under treatment with AJA (verum)

VAS ratio week 2/week 1		VAS ratio week 5/week 4	
Verum–placebo ($n = 9$)	Placebo–verum ($n = 10$)	Verum–placebo ($n = 9$)	Placebo–verum ($n = 10$)
0.30	0.58	0.54	0.22
0.53	0.60	0.74	0.52
0.55	0.82	0.79	0.64
0.55	0.94	0.94	0.72
0.62	0.99	1.01	0.88
0.67	1.04	1.14	0.89
0.85	1.07	1.21	0.94
1.04	1.09	1.22	0.99
1.08	1.10	1.24	1.01
	1.30		1.45
NNT = 2.14		NNT = 5.29	

At week 2 patients in the verum–placebo group received 20 and 40 mg AJA twice a day, respectively, patients in the placebo–verum group placebo. At week 5 patients in the placebo–verum group received 20 and 40 mg AJA twice a day, respectively, patients in the verum–placebo group placebo. Week 1 and week 4 were baseline weeks. Week 3 was the washout week. The VAS ratio is the quotient of the mean VAS scores of the treatment period and corresponding baseline week. NNT was defined as 1/(the proportion of patients successfully treated (30% pain relief) with active treatment minus the proportion of patients successfully treated with placebo).

interventions (data shown in Karst et al., 2003). No carryover or period effects were observed.

Psychotropic measurements by part B of the TMT and ARCI-M did not show significant differences over time between the two treatment groups. Mean differences in time for the TMT score were 35.89 (SD: 112.80) s in the verum–placebo group and 3.15 (SD: 63.45) s in the placebo–verum group. There was a carryover effect observed with the TMT ($p = 0.03$). Mean (SD) differences in time for the number of items answered as true by the ARCI-M were −0.67 (SD: 3.61) in the verum–placebo group and 0.22 (SD: 2.59) in the placebo–verum group (Fig. 3).

Blood pressure, temperature, pulse, breathing frequency and weight, as part of the physical parameters did not differ significantly over time. Nor did electrocardiographic, hematological- and blood-chemistry indicate any significant differences.

Doubling the dose after the fifth treatment day (day 12 and day 33) from 40 mg to 80 mg per day resulted in no significant dose response concerning pain nor did adverse effects increase. Most frequently reported adverse symptoms under active-drug were dry mouth, tiredness and dizziness (Table 4).

4. Discussion

Mechanical hypersensitivity using graded monofilaments (von Frey hairs) showed a strong tendency

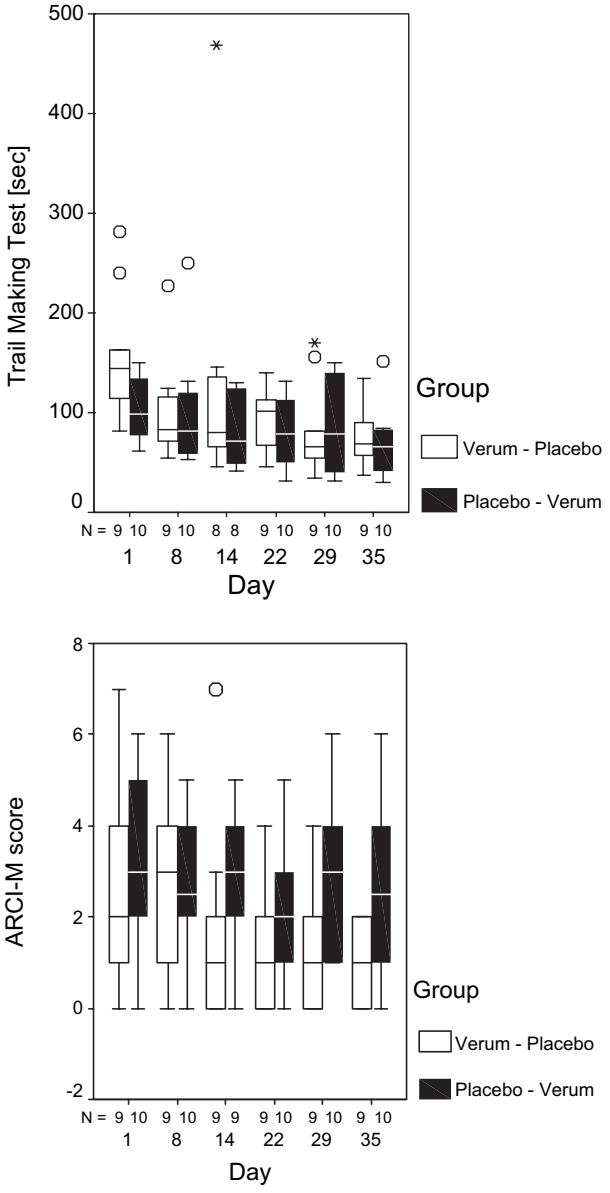


Fig. 3. Effect of AJA on psychotropic parameters. The verum–placebo group received verum (AJA) in the first treatment period (days 8–14) and placebo in the second treatment period (days 29–35). The placebo–verum group received placebo in the first treatment period and verum (AJA) in the second treatment period. Days 1 and 22 were each baseline days. Part B values of the Trail-Making Test (TMT) (measured by time to completion and number of errors) showed no significant changes over time, indicating no cognitive influences of AJA. A carryover effect, that is, the result of subjects learning to master the task more efficiently over time was also observed. Also, scores (range 0–12) for the Addiction Research Inventory-Marijuana (ARCI-M), showed no significant changes over time signifying absence of subjective drug effects by AJA. Medians (black bars), interquartile ranges (boxes), whole ranges (t-hairs), extreme values (circles) and outliers (stars) are indicated.

($p = 0.052$) towards decreasing sensitivity in the group receiving AJA *first* (verum–placebo group), although no statistically significant results were obtained. However, this tendency may become more important due to the fact that most studies failed to detect treatment effects on pain thresholds in response to mechanical or thermal stimuli (Cruccu et al., 2004). In addition, this mechanical hypersensitivity findings correspond very well to the more marked significant reduction in VAS scores under AJA in the verum–placebo group that was shown in the first report of this randomized trial (Karst et al., 2003). Since this group showed lower baseline pain levels (data shown in Karst et al., 2003) these more noticeable effects for both pain measurement tools may be interpreted as a better responsiveness towards AJA with lower baseline pain levels. Additionally, due to the immediate reinforcement, the higher motivation of patients in the verum–placebo group led possibly to the observed better treatment results. Small sample size and an excessive range of neuropathic pain clinical subgroups (central and peripheral lesions to neural structures) with differences in underlying pain mechanisms might be an explanation of why the von Frey hair test did not produce significant findings overall. Furthermore, by testing the mechanical hypersensitivity only once after intake of the drug, a time-gap that was too big between treatment- and baseline-measurements might have produced imperfect comparison values. It is therefore recommended for further studies applying the von Frey hair method that measurements be done twice on the same study day; once before and the other after administrating the test-substance. However, quantitative sensory testing may be basically associated with variability of the test–retest.

Moreover, the calculation of the NNTs with values of 2.14 and 5.29 for a 30% pain relief showed a treatment-specific effect similar to other analgesics like opioids (Watson et al., 2003) or NSAIDs (Campbell et al., 2001). However, Farrar et al. (2001) cite a 30% change in pain scores as clinically meaningful, other more conservative reports cite a 50% change in pain scores as a meaningful improvement (Moore et al., 1996). Using

Table 4
Reported side effects by patients receiving AJA treatment

Characteristic side effect	Number of reports
Dry mouth	8
Tiredness	3
Dizziness	2
Limited power of concentration	1
Sweating	1
More pain	1

From 19 patients fully completing the study, 12 reported clinically mild side effects when they received AJA (2 drop-out patients were not included). Dry mouth was the main physical and tiredness the main psychological adverse effect. Oftentimes, a combination of symptoms such as tiredness together with dry mouth were reported by patients. Consequently, the number of reports counted (16) exceeds the number of patients with adverse effects. Elevation of AJA dosage from 40 to 80 mg daily did not show a significant increase of reported side effects.

the 50% change in pain scores the NNTs would have risen to 9.00 and 10.00, respectively.

Regarding the side effect profile of the compound, our study supports the previous findings on ajulemic acid, namely, that it has no major adverse effects. The most commonly reported side effects that were seen only temporarily and only in mild to moderate degrees were dry mouth, tiredness, and dizziness that can be classified as mainly sedative side effects without broad alterations of consciousness. However, a complex pattern of altered consciousness in the sense of psychoactive effects typical for THC or Marijuana (Tart, 1971) was not observed. This is supported by the finding of no cognitive impairments, as measured by the TMT or further subjective drug effects, determined by the ARCI-M. The carryover effect as seen by the TMT score may indicate a practice result, in which subjects improved over time for each subsequent testing. Our study results are comparable with previous studies done on 24 healthy subjects with AJA, where absence of psychoactive properties was also observed (Burstein, unpublished data, 2001). Moreover, our findings argue against the assertions made in a recent preclinical report (Sumariwalla et al., 2004) predicting that AJA would be psychoactive in humans in the sense of a THC like alteration of consciousness. Their conclusion was based on limited data obtained using AJA at much higher therapeutic doses in mice. Vital or physical parameters showed no significant change over time and electrocardiography, hematological- or blood-chemistry tests did not indicate any alteration under treatment with AJA. Furthermore, raising the dose from 40 mg to 80 mg daily had an effect neither on pain reduction levels nor on numbers of reported side effects.

In summary, AJA showed a tendency towards reduced mechanical hypersensitivity in agreement with the significant pain reduction as measured by the VAS score that has been published previously (Karst et al., 2003). This synthetic cannabinoid showed no influence on physical parameters and only minor adverse subjective drug effects. Moreover, even with doses as high as 80 mg per day no complex THC or Marijuana like pattern of altered consciousness was observed. Since these promising results are based on a short-term one-week trial, further studies on AJA over longer periods are warranted.

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