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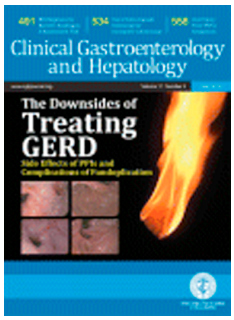

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Tetrahydrocannabinol Does not Reduce Pain in Patients With Chronic Abdominal Pain in a Phase 2 Placebo-controlled Study

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Short title: THC in chronic abdominal pain

Abbreviations: AE= adverse event; AppLe= appetite level; CB= cannabinoid receptor; CI= confidence interval; CP= chronic pancreatitis; HADS= hospital anxiety and depression scale; NRS= numeric rating scale; PASS= pain anxiety symptom scale; PCS= pain catastrophizing scale; PGIC= patient global impression of change; PK= pharmacokinetics; PSP= postsurgical pain; RAND SF-36= quality of life short form; RCT= randomized controlled trial; THC= Δ-9-tetrahydrocannabinol; TID= three times a day; TSQM= treatment satisfaction questionnaire for medication; VAS= visual analogue scale

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ABSTRACT

BACKGROUND & AIMS: Delta-9-tetrahydrocannabinol (THC) is the most abundant cannabinoid from the plant *Cannabis sativa*. There is only equivocal evidence that THC has analgesic effects. We performed a phase 2 controlled trial to evaluate the analgesic efficacy, pharmacokinetics, safety, and tolerability of an oral tablet containing purified THC in patients with chronic abdominal pain.

METHODS: Sixty-five patients with chronic abdominal pain for 3 months or more (numeric rating scale scores of 3 or more) after surgery or due to chronic pancreatitis were randomly assigned to groups given the THC tablet or identical matching placebos for 50–52 days. Subjects in the THC group were given the tablet first in a step-up phase (3 mg, 3 times daily for 5 days and then 5 mg, 3 times daily for 5 days) followed by a stable dose phase (8 mg, 3 times daily until day 50–52). Preceding and during the entire study period, patients were asked to continue taking their medications (including analgesics) according prescription. Patients reported any additional pain medications in a diary. Efficacy and safety assessments were conducted preceding medication intake (day 1), after 15 days, and at 50–52 days. Plasma samples were collected on study days 1, 15, and 50–52; mean plasma concentration curves of THC and 11-OH-THC were plotted. The primary endpoint was pain relief, measured by a visual analogue scale of the mean pain (VAS mean scores), based on information from patient diaries. Secondary endpoints included pain and quality of life (determined from patient questionnaires), pharmacokinetics, and safety.

RESULTS: At days 50–52, VAS mean scores did not differ significantly between the THC and placebo groups (F(1, 46) =.016; *P*=.901). Between the start and end of the study, VAS mean scores decreased by 1.6 points (40%) in the THC group compared to 1.9 points (37%) in the placebo group. No differences were observed in secondary outcomes. Oral THC was generally well absorbed. Seven patients in the THC group stopped taking the tablets due to adverse events, compared with 2 patients in the placebo group. All (possibly) related adverse events were mild or moderate.

CONCLUSIONS: In a phase 2 study, we found no difference between a THC tablet and a placebo tablet in reducing pain measures in patients with chronic abdominal pain. THC, administered 3 times daily, was safe and well tolerated during a 50–52 day treatment period.

Clinicaltrials.gov no: NCT01562483 and NCT01551511.

KEY WORDS: marijuana; chronic pain; AE; randomized controlled trial

INTRODUCTION

Chronic abdominal pain remains a major clinical challenge. Two typical chronic abdominal pain etiologies of visceral origin are chronic pancreatitis (CP) and postsurgical pain (PSP). Approximately 80–90% of CP patients suffer from chronic abdominal pain during the course of their illness.[1, 2] Incidences of painful post abdominal surgery adhesion development vary in literature from 45 to 90%.[3-5] Intra-abdominal adhesions are believed to be the most likely cause of PSP.[4] CP and PSP are both associated with an increased responsiveness of nociceptive pathways in the central nervous system, termed central sensitization.[6-8] Central sensitization produces pain hypersensitivity by changing the sensory response in the central nervous system, and is associated with the development and maintenance of chronic pain.[7] Because central sensitization alters the properties of neurons in the central nervous system, the pain is frequently no longer reliably coupled to the presence of particular peripheral stimuli. Therefore, pharmacologic treatment options that produce analgesia by targeting these changes in the central nervous system are required.[8]

The introduction of cannabinoids offers an interesting alternative for chronic pain management. Delta-9-tetrahydrocannabinol (THC) is the principal psychoactive compound of the *Cannabis sativa* plant,[9] and interacts with two cannabinoid receptors, termed CB1 and CB2. CB1 receptors are predominantly found in the brain and spinal cord, while CB2 receptors are located primarily in the periphery, including the immune system.[10] CB1 receptors are also highly expressed in regions critical for emotion processing including the amygdala, hippocampus, and anterior cingulate cortex.[11] Brain activity within this emotion-related circuitry was found to be increased in patients with chronic pain.[12, 13] Hence, it was suggested that cannabinoids may

modulate pain perception by disturbing the connectivity within this circuit. This was demonstrated by Lee et al., who observed that THC reduced the functional connectivity between the amygdala and the primary somatosensory cortex (S1) during pain processing.[14] Further research indicated that THC does not selectively affect these limbic regions, but rather interferes with sensory processing, which in turn reduces sensory-limbic connectivity, leading to deactivation of affective regions.[15] Thus it may be expected that THC interferes, although not selectively, with the affective components of pain.

The majority of clinical trials on the efficacy of THC for pain treatment has been focused on cancer related pain, central neuropathic pain syndromes, and acute pain conditions.[16-18] We aimed to investigate the efficacy, pharmacokinetics and safety of a novel cannabinoid-based product, an oral tablet containing purified natural THC, in patients with chronic abdominal pain.

METHODS

Study design

This phase II study used an equally randomized (allocation ratio 1:1), double-blind, placebo-controlled, parallel design. The study initially started as two clinical trials in (1) patients with painful CP and (2) patients with chronic abdominal PSP. Integration into one study was necessary due to a disappointing recruitment rate. Initial trials used identical study designs, treatment schemes and outcome parameters. Integration was supported by an independent statistician, who reviewed blinded interim data. The medical ethical committee approved both initial studies as well as the protocol amendment concerning study integration prior to study closure. The study was conducted according to the principles of the Declaration of Helsinki, and in accordance with the International Conference on Harmonization guidelines of Good Clinical Practice. All subjects provided oral and written consent before conduct of any protocol-related procedures. All authors had access to the study data and had reviewed and approved the final manuscript. Clinicaltrials.gov identification numbers NCT01562483 and NCT01551511.

Study population

Adult patients (age >18 years) suffering from abdominal pain developed after a surgical procedure or resulting from chronic pancreatitis were eligible for participation, if they had persistent or intermittent abdominal pain (on a daily basis for at least 3 months) severe enough for medical treatment (average NRS ≥ 3).[19] Key exclusion criteria were: daily cannabis use in past three years; history of hypersensitivity to THC; serious painful conditions other than PSP or CP; significant medical disorder or concomitant medication that may interfere with the study or may

pose a risk for the patient; major psychiatric illness in history; epileptic seizure in history; affected sensory input such as diabetic neuropathy; BMI >36.0 kg/m^2; significant exacerbation in illness within two weeks; positive urine drug screen or alcohol test at screening or on study days; clinically relevant abnormalities in ECG or laboratory results; pregnant or breastfeeding females; intending to conceive a child; or participation in another investigational drug study within 90 days before study entry. Preceding and during the entire study period, patients were asked to take their co-medication, including analgesics, according prescription. Patients reported additional pain medication (taken as needed) in a diary. The study was executed at the Radboud university medical center, the Netherlands. Patients were recruited by their physician or via advertisements.

Randomization and study treatment

Tablets with standardized Δ9-THC content (Namisol®, Echo Pharmaceuticals, Weesp, the Netherlands) or identical matching placebos were administered orally during a 50-52 days add-on treatment. The study treatment consisted of two phases (supplementary figure 1): a step-up phase (day 1-5: 3 mg TID; day 6-10: 5 mg TID), and a stable dose phase (day 11-52: 8 mg TID). It was permitted to taper the dosage to 5 mg TID, when 8 mg was not tolerated. Independent pharmacists dispensed either active or placebo tablets according to a computer-generated randomization list stratified for opioid and non-opioid users using separate lists. Treatment allocation was strictly concealed from participants, investigators, and all other study personnel involved in the study until end of study and database lock.

Study procedures

Efficacy and safety assessments were conducted preceding medication intake on day 1 (visit 2), after 15 treatment days (visit 3) and 50-52 treatment days (visit 4). Several phone calls were performed by the investigators during and after the treatment period (day 4-5, 9-10, 21-23, 28-30, 38-40 and 59-61) in order to evaluate the tolerability, safety and compliance.
Additional study procedures in supplementary material.

Primary efficacy outcome

The primary endpoint was change in pain intensity at the end of study treatment versus baseline of THC compared with placebo. A visual analogue scale was used in order to quantify the mean (VAS_{mean}), minimal (VAS_{min}) and maximal (VAS_{max}) pain intensity in a daily diary, starting five days preceding first medication intake until the end of study treatment. The boundaries of these 10 cm lines were 0 for no pain and 10 for unbearable pain.

Statistics primary outcome

VAS_{mean} pain was analyzed by an Analysis of Covariance (ANCOVA) of the VAS_{mean} at day 50-52 (last day of diary) between placebo and THC that incorporates VAS_{mean} at baseline (mean day -5 to -1 pre-treatment) as covariate in the analyses. Possible moderating variables such as subpopulation (pancreatitis/postsurgical) and opiate user (y/n) were evaluated by observing potential interactions and post hoc subgroup analyses.
Secondary outcomes and statistics are fully described in supplementary material.

RESULTS

A total of 69 patients were assessed for eligibility during screening, of whom 65 were included and randomized (figure 1). Sixty-two patients started study medication, of whom 21 (8 CP/ 13 PSP) patients in the THC arm and 29 (15 CP/ 14 PSP) patients in the placebo arm were included in the modified intention to treat efficacy analysis. For the safety analysis, 30 (12 CP/ 18 PSP) patients were included in the THC arm and 32 (15 CP/ 17 PSP) patients in the placebo arm. Eligible patients were recruited from October 2012 to July 2014, and stopped due to poor recruitment.

Efficacy

For patients in the efficacy analyses, mean (SD) VAS_{mean} pain scores at baseline were 4.0 (1.9) and 5.2 (1.8) for THC and placebo respectively, and for patients in the safety analysis, including drop-outs, 4.3 (1.9) and 5.2 (1.9) points respectively. VAS_{mean} pain scores during THC and placebo treatment are shown in figure 2. Primary efficacy analysis of the average VAS pain at the last day of diary did not reveal significant difference between THC and placebo treatment (95% CI of diff [-1.31, 1.16], $F(1, 46) = .016$, $p = .901$). Mean VAS pain scores were reduced on average of 1.6 points (40%) in the THC arm compared to 1.9 points (37%) in the placebo arm. Parallel results were observed for minimal and maximal reported VAS pain. Subgroup analyses of CP (95% CI of diff [-2.23, 1.78], $F(1, 19) = .056$, $p = .816$) and PSP (95% CI of diff [-1.87, 1.70], $F(1, 24) = .010$, $p = .922$) patients revealed similar results and did not affect these outcomes as covariate. VAS pain outcomes are presented in table 2.

Secondary efficacy outcomes

No statistically significant differences were observed in pain related questionnaires such as the patient global impression of change, pain catastrophizing or pain related anxiety. Measures of depression and generalized anxiety, quality of life, treatment satisfaction did also not change after THC treatment compared with placebo. For the domain pain of the SF-36 a trend was observed in favor of THC ($F(1, 47) = 4.023$; $p = .051$). Additionally, no differences were observed in subjective feelings corresponding to alertness, mood and calmness nor for psychedelic effects including difficulties in controlling thoughts, feeling high and feeling drowsy for THC compared with placebo.

No statistically significant differences between THC and placebo were observed for appetite level. Subjects in the THC group gained on average 0.8 kg in weight and patients in the placebo group lost on average 0.4 kg during study treatment (NS ($F(1, 47) = 1.711$; $p = .197$)). Balance disturbances were shown in several individuals, but did not statistically increase during THC treatment compared with placebo.

Pharmacokinetics

PK samples on day 50-52 time-locked after medication intake were analysed for 19 (8 CP/ 11 PSP) subjects resulting in 14 PK profiles of 8 mg and 5 PK profiles of 5mg THC. Mean THC plasma concentration curves of THC and 11-OH-THC were plotted (supplementary figure 2). Evaluation of the pharmacokinetics at an individual patient level revealed that some patients demonstrate a relatively late t_{max} accompanied with a relatively low C_{max} , which cannot be observed in the plasma concentration curves. Table 3 summarizes the calculated PK parameters of THC and 11-OH-THC. The t_{max} of THC was 1.4 hours in patients on 8mg TID compared with 1.8 hours in patients on 5mg TID Namisol® regimen, and the $t_{1/2term}$ was 3.1 hour and 3.3 hour respectively.

Mean (± SD) trough levels for THC were 0.70 (± .59) ng/mL on day 15 and 0.57 (± .32) ng/mL on day 50-52. One patient demonstrated predose concentration levels below the lower limit of quantification on day 15.

Safety

Seven patients administering THC discontinued study treatment due to AEs compared with 2 patients in the placebo group. These patients did not tolerate a dosage of 5 mg TID THC and withdrew due to mild to moderate AEs. Another 5 patients in the THC arm, compared with 2 patients in the placebo arm, tapered their dosage to 5 mg TID.

A summary of (possibly) related AEs are presented in table 4. Five patients experienced serious AEs during the study treatment that were all considered not to be related to the study drug. Further AEs were mild or moderate. All subjects fully recovered from AEs. There were no clinically relevant changes in vital signs, ECG parameters, or safety laboratory parameters (hematology, biochemistry, and urinalysis).

Treatment compliance

A mean (± SD) of 97% (± 4%) of all placebo study medication was taken correctly compared with 98% (± 2%) in the THC treatment arm. There were no patients with a poor compliance (<75%), as measured by the amount of medication returned to the hospital after the treatment period. One subject appeared to be not compliant according PK predose levels on day 15, but demonstrated regular trough levels on day 50.

DISCUSSION

This is the first exploratory study to evaluate the analgesic efficacy, pharmacokinetics and tolerability of THC, 1) using an oral tablet with improved bioavailability and optimal blinding potential, 2) in patients with chronic abdominal pain, 3) during a relatively long-lasting treatment period of 50 days.

Contrary to our hypothesis, THC did not show a beneficial effect on chronic abdominal pain compared with placebo. Similar results were observed for minimal and maximal reported VAS pain, indicating that THC does not affect background pain or pain peaks. It should be mentioned that, despite the randomization procedure, patients in the THC group demonstrated pain of 1.2 points lower intensity at baseline than patients in the placebo group. In addition to the primary outcome, several questionnaires were used to evaluate a wide range of secondary efficacy outcomes during and after the THC treatment period. No differences were observed in pain related questionnaires or measures of depression and anxiety, quality of life and treatment satisfaction.

There are many reasons why clinical trials may fail to demonstrate analgesic efficacy on the primary endpoint. In first instance this could be related to insufficient analgesic potency of the investigational drug, but it may also be related to 1) an impaired bioavailability, 2) a large placebo response, 3) indirect analgesic effects, or 4) an inadequate study design.

The absorption of orally administrated drugs might be affected particularly in patients with gastrointestinal deficits.[20] In the present study, mean plasma concentration curves of patients on both 5 mg as well as 8 mg TID treatment regimen demonstrate that THC was generally well absorbed and further metabolized into 11-OH-THC. The

t_{max} of THC was 1.4 hour in patients on 8mg TID compared with 1.8 hour in patients on 5mg TID THC regimen. This delay in absorption in patients on 5mg TID THC was accompanied with an enhanced $t_{1/2term}$ duration, which overall resulted in comparable $AUC_{0\text{-}tau}$ between the two treatment regimens. It should be mentioned that the PK sampling until 6 hours postdose was too short for two patients on 5mg TID THC in order to obtain all elimination parameters. So these parameters are probably an underestimation. However, the reliable pharmacokinetic profiles observed in our study population do not explain the lack of observed efficacy.

A large placebo response of 37% pain reduction was observed in current study, which is common in chronic visceral pain studies. A meta-analysis including 8.364 patients with irritable bowel syndrome allocated to placebo observed a pooled placebo response of 37.5%.[21] However, a previous RCT of our study group also observed a high reduction of average pain score by 24% in the placebo arm, but this did not prevent proof of superiority of pregabalin over placebo using a very similar study design in patients with CP.[22] Underlying mechanisms of the placebo effect can be derived from psychological and neurobiological viewpoints. Two well supported mechanisms from a psychological point of view are expectancy and conditioning.[23] Factors that influence the magnitude of the placebo response in RCTs include type of active medication, randomization ratio, and the number of planned face-to-face visits, thereby supporting the expectancy hypothesis.[24] High expectations toward treatment efficacy of THC might have contributed to the substantial placebo response as observed in the present study.

The lack of observed analgesic efficacy can also be considered from a mechanistic point of view. Two major mechanisms are currently proposed to underlie chronic pain and its development: 1) sensitization of nociceptive processing (central sensitization/ hyperalgesia), and 2) alterations in central cognitive and autonomic processing.[8, 13] Consequently, the focus of treatment options for chronic pain has been shifting away from targeting the anatomical site to targeting changes in the peripheral and central nervous system. The anti-hyperalgesic potential of THC is not clearly demonstrated in human and should be further evaluated using measurements such as quantitative sensory testing or EEG.

Patients with persistent pain demonstrated increased brain activity in areas considered to mediate emotion including the perigenual anterior cingulate cortex, the medial prefrontal cortex, and parts of the amygdala.[13] Thus, the representation of pain in the brain shifts over time to areas implicated in cognitive function, particularly emotion.[25] The frontal-limbic distribution of cannabinoid receptors in the brain suggests that cannabis may preferentially target the affective qualities of pain. A study conducted by Lee et al. demonstrated that dronabinol reduced the reported unpleasantness, but not the intensity of ongoing pain and hyperalgesia.[14] This suggests a shift in central nervous system function from nociceptive to cognitive, affective and autonomic sensitization in patients moving from acute to chronic pain. Therefore, an agent targeting particular brain areas related to the cognitive emotional feature of chronic pain, such as THC, might be efficacious in our chronic pain population, but might be better measured using affective outcomes of pain.

In general, THC was well tolerated resulting in only mild to moderate (possibly) related adverse events, which were similar to previous studies in CP patients and

healthy volunteers.[26, 27] The considerable number of AEs reported in the placebo group as well as the withdrawal of patients because of AEs, despite being in the placebo arm, indicate that AEs were partly determined by nonpharmacological effects.[28, 29] This so called nocebo effect induces negative effects due to negative expectations. Cannabis is a generally well known product, particularly as recreational drug to induce desired psychotropic effects such as euphoria, relaxation, and perceptual alterations. Therefore, it is plausible that patients in this study were influenced by expectations, which may have influenced the occurrence of AEs.

A major limitation of the present study is the small sample size, which is insufficiently large to allow subgroup analyses. However, considering the confidence intervals of the effect, it is doubtful that an increased sample size would have been resulted in significant differences.

Furthermore, the present study comprises a heterogeneous patient population regarding etiology and anatomical site of the pain. However, all patients suffered from chronic abdominal pain, which is associated with central sensitization and alterations in central cognitive and autonomic processing.[8, 13] The presence of central sensitization in chronic pain patients supports the choice of treatments that reduce pain by normalizing hyperexcitable central neural activity, which makes the initial pain etiology or peripheral stimulus and past or currently received pain treatments less important. These variables and other patient characteristics might have contributed to inter-individual differences in treatment effects – while on the other hand enhancing the generalizability of the study.

Additionally, it should be mentioned that most patients already had received different pain treatments including analgesics, which failed to provide a satisfactory level of

pain relief. Thus, this study included a selection of patients who did not respond to registered analgesics with a proven efficacy.

In summary, we conclude that THC treatment showed acceptable safety and tolerability profiles during a 50-52 day add-on treatment period, but did not significantly reduce pain scores or secondary efficacy outcomes in patients with chronic abdominal pain compared to placebo. Further research should evaluate the the effects of THC on secondary and tertiary central pain processing.

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FIGURE LEGEND

Figure 1: Participant flowchart.

Figure 2: Mean VAS pain at baseline (day -5 to -1) and during study treatment (day 1 to 49) for THC and placebo in patients with chronic abdominal pain (n=50), subdivided in chronic pancreatitis (n=23) and postsurgical pain (n=27). VASpain scores are shown until day 49, which is the last day of diary for most patients. Grey bars represent baseline period.

Supplementary material: figure 1. After baseline measurements, patients administrated 3 mg TID THC or placebo from day 1 to 5. On day 5, tolerability was evaluated. The dosage of day 6 to 10 was increased to 5 mg TID or, when not tolerated, the patient was withdrawn. On day 10, the tolerability was evaluated again. From day 11 to 15, the dosage was further increased to 8 mg TID. This dosage could be tapered to 5 mg TID, when 8 mg appeared to induce unacceptable adverse events (dotted arrows). At day 15 the tolerability was evaluated again. If tolerable, patients proceeded with 8 mg TID, but if not, the dosage was reduced to 5 mg TID. Grey filled arrows represent decision points I en II: increased dosage or withdrawal. Black filled arrow represents decision point III: continue 8 mg TID, taper to 5 mg TID, or withdrawal. Dotted line represents the permitted dose adjustment of minimal 5 mg TID.

Supplementary material: figure 2. Mean (unilateral SD error bars) plasma concentration curves of THC and 11-OH-THC obtained after 50-52 treatment days in chronic abdominal pain subjects taking 5 mg versus 8 mg TID THC

Table 1: Demographic and clinical characteristics.

	Chronic Pancreatitis (n=23)		Postsurgical pain (n=27)	
	THC	**Placebo**	**THC**	**Placebo**
Gender (male/female)	7/1	11/4	2/11	5/9
Age (years)	53.9 (7.5)	53.9 (10.3)	52.2 (11.3)	51.9 (8.2)
BMI (kg/m2)	24.2 (5.0)	24.3 (3.8)	27.0 (4.5)	26.4 (3.5)
Ethnicity				
Caucasian	8	14	12	14
Mixed Afro-Caucasian	0	0	1	0
Asian	0	1	0	0
NRS pain at screening	5.3 (1.7)	5.9 (1.6)	6.9 (1.0)	7.0 (0.8)
Concomitant medication				
None	0	0	0	2
PCM	3	12	12	10
NSAID	3	2	5	1
Weak opioids	3	6	5	7
Strong opioids	7	11	4	4
Antiepileptics	3	4	1	3
Smoking status				
Current smoker	6	6	4	6
Past smoker	1	6	1	5
No smoker	1	3	8	3
Etiology CP				
Alcohol	6	3		
Hereditary	0	1		
Idiopathic	2	7		
Neoplasm	0	2		
Other	0	2		

Continuous data are expressed as mean (SD) and categorical data as numbers (n). Weak opioids were defined as codeine and tramadol. Strong opioids were defined as opioid-based therapies such as oxycontin, fentanyl and morphine. Abbreviations: PCM=paracetamol, NSAID= non-steroidal anti-inflammatory drugs.

Table 2: VAS pain scores

		Mean VAS pain		Minimal VAS pain		Maximal VAS pain	
		Mean	SD	Mean	SD	Mean	SD
Chronic abdominal pain (n=50 modified ITT analysis)							
THC	Baseline	4.0	1.85	2,79	1,53	4,61	2,39
	Last day	2.4	2.28	1,75	1,97	4,20	2,78
	Mean last 5 days	2.9	2.13	1,85	1,76	4,61	2,39
	Diff (last day minus baseline)	-1.6	1.78	-0,96	1,77	-0,40	0,85
Placebo	Baseline	5.2	1.75	3,03	1,85	5,66	2,24
	Last day	3.5	2.42	2,54	1,98	5,44	2,63
	Mean last 5 days	3.8	2.20	2,61	1,75	5,66	2,24
	Diff (last day minus baseline)	-1.9	2.18	-0,87	1,14	-0,12	1,50
Chronic abdominal pain (n=62 including drop-outs)							
THC	Baseline (including drop-outs)	4.3	1.93	3,28	1,98	4,61	2,39
Placebo	Baseline (including drop-outs)	5.2	1.89	3,12	2,52	5,66	2,24
Chronic Pancreatitis (n=23)							
THC	Baseline	3.4	2.32	1,84	1,41	4,64	2,64
	Last day	1.7	2.56	1,26	1,65	4,03	3,22
	Mean last 5 days	3.1	2.81	1,46	1,71	4,64	2,64
	Diff (last day minus baseline)	-1.7	1.61	-0,70	0,77	-0,57	0,94
Placebo	Baseline	4.9	1.94	2,80	2,23	5,58	2,23
	Last day	3.1	2.23	2,25	1,95	4,98	3,06
	Mean last 5 days	3.6	2.09	2,31	1,75	5,58	2,23
	Diff (last day minus baseline)	-2.1	2.28	-1,01	1,31	-0,40	1,76
Postsurgical pain (n=27)							
THC	Baseline	4.4	1.48	3,26	1,40	4,59	2,34
	Last day	2.8	2.08	2,01	2,14	4,28	2,65
	Mean last 5 days	2.8	1.70	2,04	1,82	4,59	2,34
	Diff (last day minus baseline)	-1.5	1.94	-1,07	2,08	-0,30	0,82
Placebo	Baseline	5.6	1.54	3,28	1,37	5,74	2,34
	Last day	3.9	2.61	2,82	2,03	5,88	2,18
	Mean last 5 days	3.9	2.37	2,89	1,78	5,74	2,34
	Diff (last day minus baseline)	-1.7	2.16	-0,74	0,99	0,13	1,22

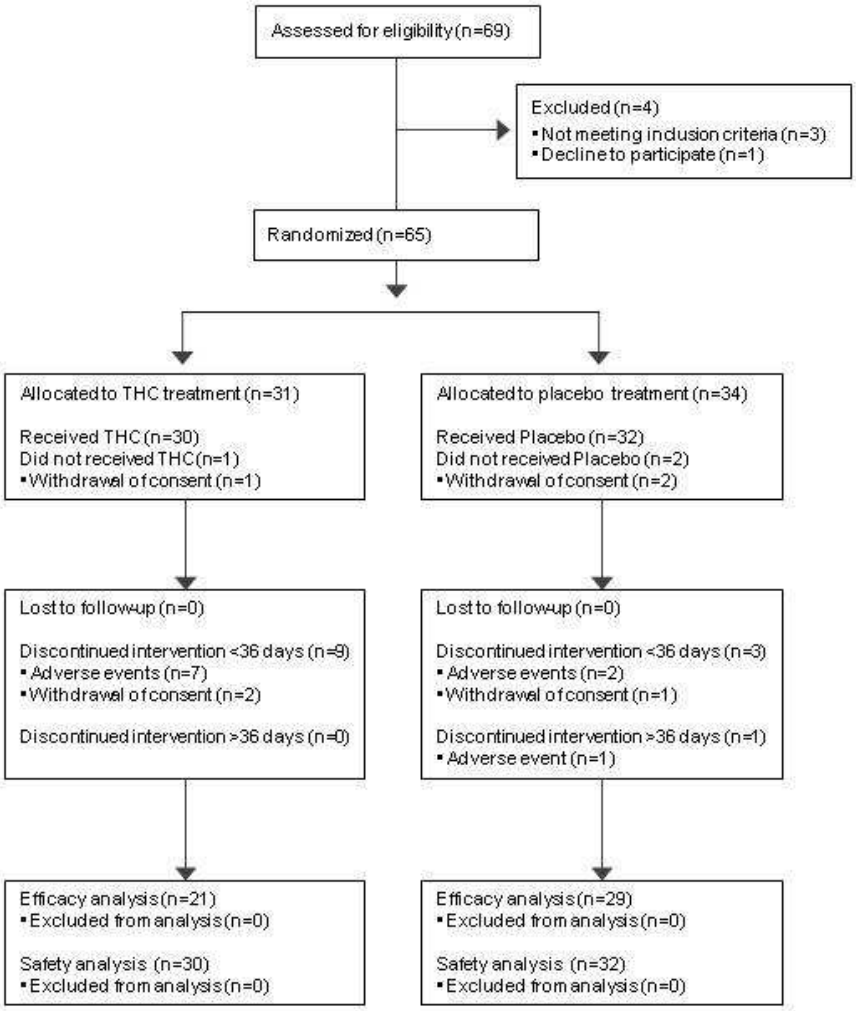
Table 3: Pharmacokinetic parameters of THC and 11-OH-THC after 50-52 days oral dosing of 8 mg or 5 mg TID THC in patients with chronic abdominal pain

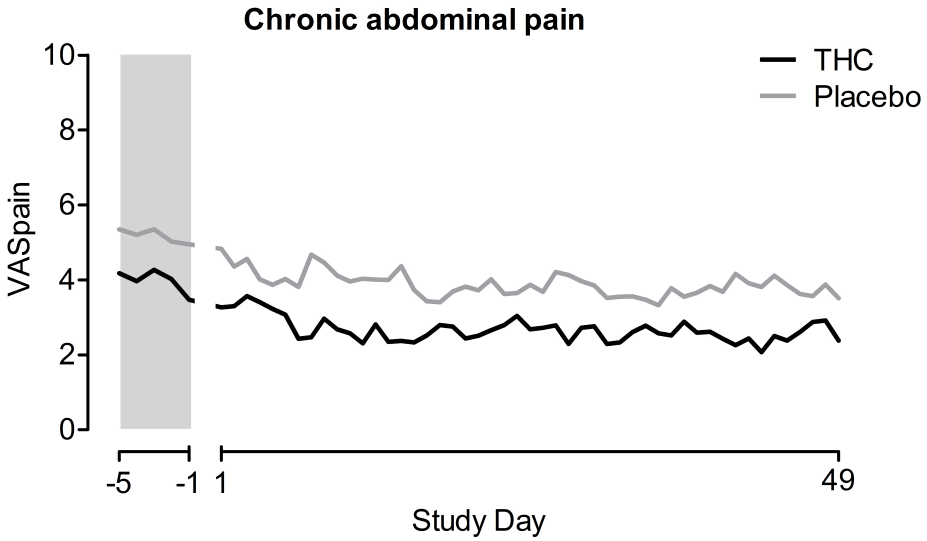
	THC 8 mg TID			THC 5 mg TID		
	N	**Mean**	**SD**	**N**	**Mean**	**SD**
THC						
C_{max} (ng/mL)	14	5,21	2,51	5	4,35	2,65
t_{max} (h)	14	1,43	1,52	5	1,78	1,72
AUC $_{0\text{-}Last}$ (ng*h/mL)	14	9,89	3,23	5	8,62	2,96
AUC $_{0\text{-}tau}$ (ng*h/mL)	13	11,01	3,42	3	10,56	2,55
$t_{1/2term}$ (h)	13	3,10	1,27	3	3,32	1,89
11-OH-THC						
C_{max} (ng/mL)	14	6,89	2,97	5	5,50	1,54
t_{max} (h)	14	1,58	1,31	5	2,22	1,32
AUC $_{0\text{-}Last}$ (ng*h/mL)	14	19,32	8,44	5	19,03	6,25
AUC $_{0\text{-}tau}$ (ng*h/mL)	12	20,15	8,37	3	22,13	8,04
$t_{1/2term}$ (h)	12	2,82	0,75	3	4,52	2,41

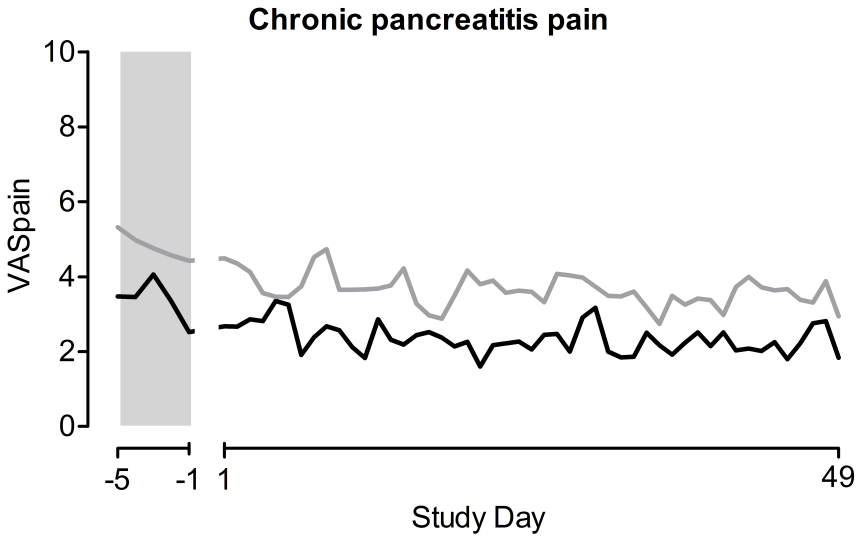
AUC $_{0\text{-}inf}$, AUC $_{0\text{-}tau}$, $t_{1/2term}$ and λ_z were calculated only if there were two or more points (excluding C_{max}) in the elimination phase of the plasma concentration–time curve with r^2>0.80.

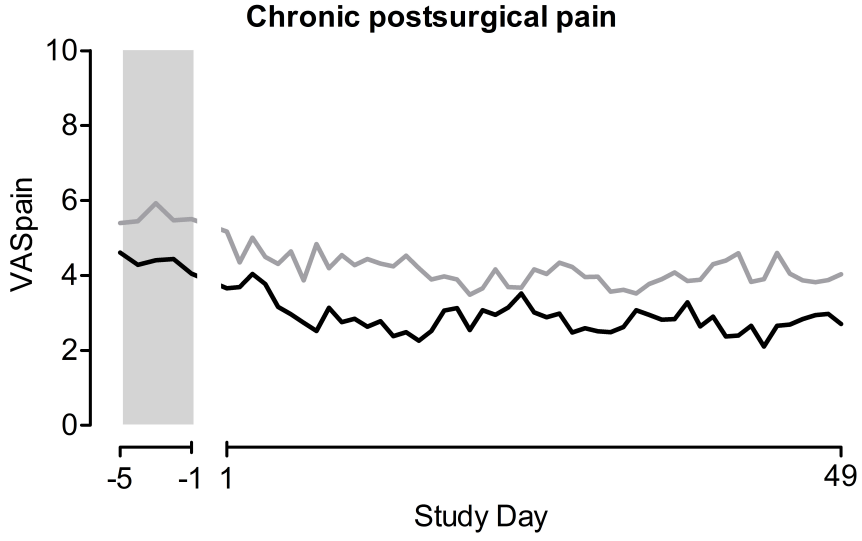
Table 4: Summary of (possibly) related adverse events occurring in ≥10% patients treated with THC or placebo included in the safety analyses (n=62). All (possibly) related adverse events were mild to moderate.

	THC (n=30)		Placebo (n=32)	
Averse events (PT term MedDRA)	N	%	N	%
General				
Decreased appetite	6	20%	1	3%
Increased appetite	7	23%	6	19%
Nervous system disorders				
Amnesia	4	13%	1	3%
Balance disorder	3	10%	4	13%
Disturbance in attention	4	13%		
Dizziness	24	80%	11	34%
Dysgeusia	3	10%	1	3%
Headache	14	47%	18	56%
Somnolence	15	50%	11	34%
Psychiatric disorders				
Confusional state	3	10%	3	9%
Depressed mood	3	10%	2	6%
Euphoric mood	4	13%	2	6%
Irritability	2	7%	2	6%
Sluggishness	3	10%		
Gastro-intestinal system disorders				
Abdominal pain	3	10%		
Constipation	4	13%	5	16%
Diarrhoea	3	10%	2	6%
Dry Mouth	9	30%	2	6%
Nausea	13	43%	5	16%
Skin and subcutaneous tissue disorders				
Hyperhidrosis	8	27%	5	16%
Rash			5	16%
Musculoskeletal and connective tissue disorders				
Tremor	1	3%	4	13%
Vision disorders				
Visual impairment	4	13%	1	3%


Assessed for eligibility (n=69)
Excluded (n=4)
▪ Not meeting inclusion criteria (n=3)
▪ Decline to participate (n=1)
Randomized (n=65)
Allocated to THC treatment (n=31)
Received THC (n=30)
Did not received THC (n=1)
▪ Withdrawal of consent (n=1)
Allocated to placebo treatment (n=34)
Received Placebo (n=32)
Did not received Placebo (n=2)
▪ Withdrawal of consent (n=2)
Lost to follow-up (n=0)
Discontinued intervention <36 days (n=9)
▪ Adverse events (n=7)
▪ Withdrawal of consent (n=2)
Discontinued intervention >36 days (n=0)
Lost to follow-up (n=0)
Discontinued intervention <36 days (n=3)
▪ Adverse events (n=2)
▪ Withdrawal of consent (n=1)
Discontinued intervention >36 days (n=1)
▪ Adverse event (n=1)
Efficacy analysis (n=21)
▪ Excluded from analysis (n=0)
Safety analysis (n=30)
▪ Excluded from analysis (n=0)
Efficacy analysis (n=29)
▪ Excluded from analysis (n=0)
Safety analysis (n=32)
▪ Excluded from analysis (n=0)


Chronic abdominal pain
THC
Placebo
VASpain
10
8
6
4
2
0
-5
-1
1
49
Study Day


Chronic pancreatitis pain
VASpain
10
8
6
4
2
0
-5
-1
1
49
Study Day


Chronic postsurgical pain
VASpain
10
8
6
4
2
0
-5
-1
1
49
Study Day

Supplementary material 1: Methods

Study procedures

Potential participating patients were screened for eligibility within 7-35 days prior to start of study treatment (visit 1). Screening included demographics, medical history, concomitant medication, smoking habits, physical examination, 12-lead electrocardiogram (ECG), standard laboratory blood tests (hematology, biochemistry, virology) and urine screening tests (urinalysis, drug screening and pregnancy test). Furthermore, all patients received a diary to report pain scores, add-on analgesics and adverse events.

Study days were carried out at the clinical research center of the Radboudumc, where each patient stayed in a separate quiet room.

Secondary efficacy outcomes

Pain related questionnaires included the patient global impression of change (PGIC)[1] evaluated on day 15 and 50-52, pain catastrophizing scale (PCS)[2, 3] evaluated on day 1, 15 and 50-52, and pain anxiety symptom scale (PASS)[4] evaluated on day 1 and 50-52. The hospital anxiety and depression scale (HADS)[5], and quality of life questionnaire (RAND SF-36)[6] were filled out at day 1 and 50-52. Treatment satisfaction (TSQM v. II)[7] and the patient appetite level (AppLe) were evaluated at the last study visit. The AppLe was a modification of the PGIC to evaluate any change in appetite in the last week and compared to before the study period.

Drug effects on alertness, mood, and calmness were explored using the Bond & Lader questionnaire, and potential subjective psychotomimetic (psychedelic) effects were evaluated using the Bowdle questionnaire.[8, 9] Both questionnaires were filled

out on day 1, 4-5, 9-10, 15, and 50-52.

Left-right (roll) and anterior-posterior (pitch) postural movements were measured using a gyroscope-based measurement system (SwayStar™, Balance International Innovations GmbH, Switzerland), which was attached to the waist of the patient. Patients stood, without shoes, as still as possible in a standardized base of support with their arms hanging at both sides of their body. Body sway was measured for one minute with eyes open, one minute with eyes closed and for 30 seconds with eyes open standing on one leg of preference. Patients were asked to fixate at one point during the tasks with eyes open. The computerized measures used for analysis reflect the total angular area and 90% range roll and pitch excursion in degrees from the centre of gravity.

Safety and Tolerability

Safety and tolerability were evaluated using spontaneously reported adverse events (AEs) and measurements of vital functions, ECG and laboratory tests. AEs were recorded in a daily diary, at study visits and phone calls up to 2 weeks after study drug discontinuation. Blood pressure and heart rate were measured at screening and on both study days. ECG, hematology, blood chemistry, and urinalysis were performed at screening and at the end of the study.

Pharmacokinetics

Plasma concentrations of THC and its active metabolite 11-OH-THC were determined predose on day 1, 15 and 50-52 to confirm a baseline state, determine trough levels and test the compliance. The PK sampling on day 50-52 was extended with 7 additional samples time-locked after medication intake at 0:30, 1:00, 2:00,

3:00, 4:00, 5:00, and 5:55 hours postdose. Blood samples were collected in 4ml EDTA tubes and immediately after collection wrapped in aluminum foil and kept on ice. Samples were centrifuged within 30 minutes at 2000 g for 10 minutes at 4℃. The handling of THC samples was done avoiding direct light. The separated plasma was divided into primary and backup samples, and stored at –80℃ until bioanalysis. Bioanalysis (Analytisch Biochemisch Laboratorium b.v., Assen, the Netherlands) was performed using a validated liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) assay method according to good laboratory practice procedures. The lower limit of quantification for THC and 11-OH-THC was 0.100 ng ml^{-1}.

Statistical analysis

The primary outcome of this study was change in pain intensity, measured by the VAS_{mean} in a daily diary, between THC and placebo treatment. VAS_{mean} pain was analyzed by an Analysis of Covariance (ANCOVA) of the VAS_{mean} at day 50-52 (last day of diary) between placebo and THC that incorporates VAS_{mean} at baseline (mean day -5 to -1 pre-treatment) as covariate in the analyses. Possible moderating variables such as subpopulation (pancreatitis/postsurgical) and opiate user (y/n) were evaluated by observing potential interactions and post hoc subgroup analyses. Secondary efficacy outcomes were analyzed in a similar manner. All participants who received the study medication for at least 36 days were included in the efficacy analyses according to the intention to treat principle. Dropouts before day 36 were replaced and data of dropouts were excluded from further analyses for efficacy. Safety analyses was performed on all randomized subjects who received at least one dose of THC or placebo.

For statistical analysis SPSS software for Windows v.20 was used. All statistical tests were performed two-tailed, and the limit for statistical significance was set at $P<0.05$. The initial study in CP patients was powered ($\alpha = 0.05$, power = 0.80) to detect a decrease of at least 1.0 VAS_{mean} pain in the THC group compared with placebo, resulting in 34 patients per group. Variances in pain scores were extrapolated from a similar study with pregabalin.[10] No information was available to estimate the SD in the initial PSP study, therefore, same numbers were adopted for this study. Input variances for the integrated study were considered to be too unreliable to conduct a sample size calculation. Therefore, no sample size calculation was performed for this early phase 2 clinical trial.

Non-compartmental analysis to determine plasma PK parameters of the active compounds, THC and 11-OH-THC, was performed using the WinNonlin modeling and analysis software (version 2.1 a; Pharsight Inc., Apex, NC). The maximum plasma concentration (C_{max}), the time to reach C_{max} (T_{max}), and the AUC from 0 up to the last measurement (AUC_{0-last}, using the linear log trapezoidal rule) were calculated from the individual plasma concentration-versus-time profiles. The terminal half-life ($t_{1/2\ term}$) was calculated only if there were two or more points (excluding C_{max}) in the elimination phase of the plasma concentration–time curve with $r^2>0.80$. For that reason, one patient was excluded from this part of the analysis for THC and two patients for 11-OH-THC. Subsequently, the areas under the plasma concentration curves extrapolated to the end of the dosing period (AUC_{tau}) were calculated using the linear log trapezoidal rule and extrapolation to 8 hours.

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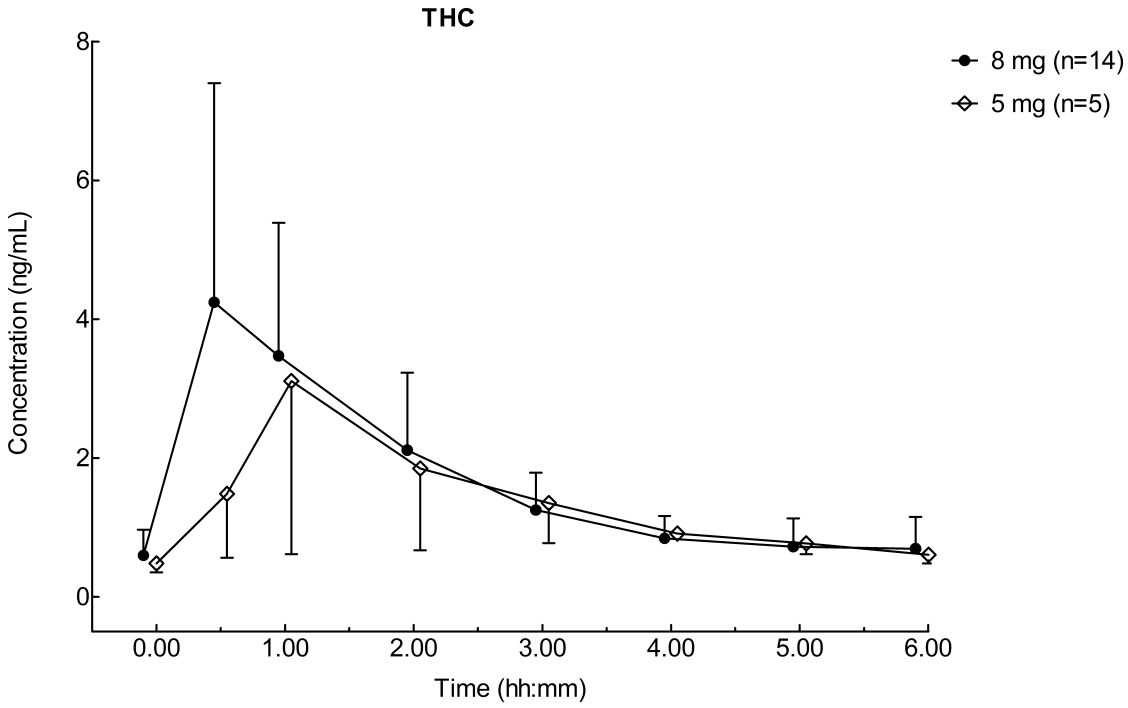
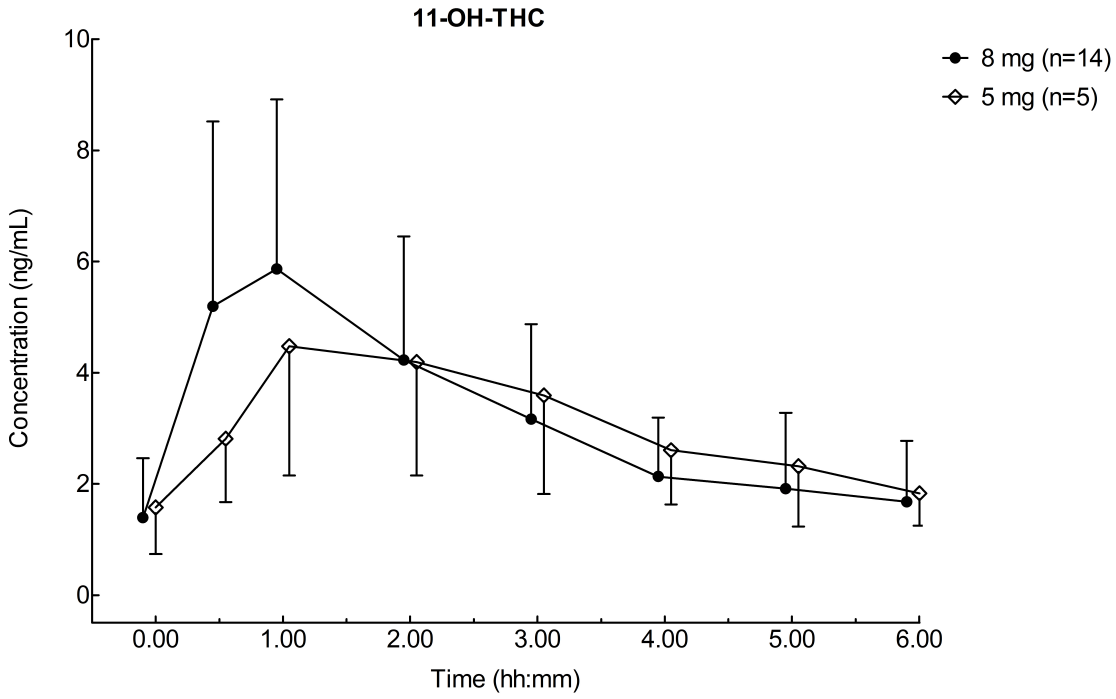

THC
8 mg (n=14)
5 mg (n=5)
Concentration (ng/mL)
0
2
4
6
8
0.00
1.00
2.00
3.00
4.00
5.00
6.00
Time (hh:mm)


11-OH-THC
8 mg (n=14)
5 mg (n=5)
Concentration (ng/mL)
0
2
4
6
8
10
0.00
1.00
2.00
3.00
4.00
5.00
6.00
Time (hh:mm)