Characterization and re-evaluation of experimental pain models in healthy subjects

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Chapter 6

EFFECT PROFILE OF PARACETAMOL, Δ9-THC AND PROMETHAZINE USING AN EVOKED PAIN TEST BATTERY IN HEALTHY SUBJECTS

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ABSTRACT

A battery of evoked pain tasks (PainCart) was developed to investigate the pharmacodynamic properties of novel analgesics in early phase clinical research. As part of its clinical validation, compounds with different pharmacological mechanisms of actions are investigated. The aim was to investigate the analgesic effects of classic and non-classic analgesics compared to a sedating negative control in a randomized placebo-controlled crossover study in 24 healthy volunteers using the PainCart.

The PainCart consisted of pain tasks eliciting electrical, pressure, heat, cold and inflammatory pain. Subjective scales for cognitive functioning and psychotomimetic effects were included. Subjects were administered each of the following oral treatments: paracetamol (1000 mg), Δ9-THC (10 mg), promethazine (50 mg) or matching placebo. Pharmacodynamic measurements were performed at baseline and repeated up to 10 hours post-dose.

Paracetamol did not show a significant reduction in pain sensation or subjective cognitive functioning compared to placebo. Promethazine induced a statistically significant reduction in PTT for cold pressor and pressure stimulation. Furthermore, reduced subjective alertness was observed. Δ9-THC showed a statistically significant decrease in PTT for electrical- and pressure stimulation. Δ9-THC also demonstrated subjective effects, including changes in alertness and calmness, as well as feeling high and psychotomimetic effects.

This study found a decreased pain tolerance due to Δ9-THC and promethazine, or lack thereof, using an evoked pain task battery. Pain thresholds following paracetamol administration remained unchanged, which may be due to insufficient statistical power. We showed that pain thresholds determined using this pain test battery are not driven by sedation.

INTRODUCTION

The complex clinical reality of pain medicine demands novel therapeutics. A multi-modal battery of evoked pain tasks could be a useful tool to investigate the analgesic properties of novel compounds, but needs to be pharmacologically validated for specific classes of compounds. In the present study the effects of three oral drugs were investigated and compared to placebo: Δ9-tetrahydrocannabinol (Δ9-THC), paracetamol and promethazine.

Different cannabinoids have previously been shown to be effective in various pain conditions, including neuropathic pain related to oncological disease.[55] Δ9-THC has been shown to be an effective analgesic in preclinical studies and clinical trials. However, previous formulations of cannabinoid Δ9-THC are also known for variable pharmacokinetic profiles and pharmacodynamic responses.[22] To overcome barriers in clinical application, novel formulations and cannabinoids are under development.[23]

Even though paracetamol is one of the most widely used medications in the world, there is still debate regarding its exact mechanism of action. Paracetamol is thought to be a weak inhibitor of prostaglandins (PG) synthesis. The subsequent main driving mechanism of paracetamol analgesia is not completely understood. It has been proposed that it exerts most of its effects through COX-2 inhibition, but also inhibition of endocannabinoids has been proposed. In addition, various neurotransmitter systems (*e.g.*, serotonergic, opioid and noradrenaline) are thought to be involved.[8,11,19,24]

To investigate the role of sedation rather than analgesic effects of psychoactive compounds a negative control was included in the current study in the form of the H1 antihistaminergic promethazine (50 mg). Even though it has been observed in preclinical research that H1 antihistaminergic drugs may have analgesic potential, this has not been replicated in clinical practice for oral formulations administered alone.[44,48] Therefore we considered this sedative compound suitable as a comparator drug without analgesic effects

The primary aim of this study is to investigate the analgesic effects of classic and non-classic analgesics compared to a sedating negative control in a randomized placebo-controlled crossover study in 24 healthy volunteers using the PainCart. As a secondary objective, by comparing the effects of the 3 compounds within each subject in a crossover design, and comparing the analgesic profile to the profiles of other analgesic compounds that we recently investigated using the battery of evoked pain tasks, we aimed to further elucidate the still unknown pharmacological mechanism of action of Δ9-THC and paracetamol analgesia.

The battery of evoked pain tasks has been pharmacologically validated by investigating a broad range of analgesics from various classes, with diverse but well-known mechanisms of action.[40] This first pharmacological validation study demonstrated the necessity of utilising a range of pain tasks in early-phase drug research. Namely, each compound provided a unique fingerprint of effects on the test battery. These findings emphasized the importance of utilising a range of pain tasks, rather than a single pain task, when determining the profile of analgesic effects of a compound in early phase drug development. Building on this knowledge, the present study investigated the effects of two (classes of) analgesics, paracetamol and Δ9-THC, and additionally the effects of sedation using promethazine as a negative control.

METHODS

Subjects and study design

The study was a double blind, double-dummy, single dose, randomized, placebo-controlled, crossover study in which the effects of paracetamol, Δ9-THC and the negative control promethazine were compared to placebo. The study was conducted at the Centre for Human Drug Research in Leiden, The Netherlands. The study was approved by the Medical Ethics Committee of Stichting Beoordeling Ethiek Biomedisch Onderzoek (Assen, The Netherlands) and was conducted according to the Dutch Act on Medical Research Involving Human Subjects (WMO) and in compliance with all International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines and the Declaration of Helsinki. This study was registered in the public registry of the Centrale Commissie Medisch Onderzoek (CCMO) in the Netherlands, under registration number: NL54643.056.15

Each subject provided written informed consent before any screening procedures were performed. A total of 24 healthy subjects (12 males and 12 females) between 18 and 45 years of age with a body mass index of 18 to 30 kg/m² were enrolled. The subjects underwent a full medical screening, including medical history anamnesis, a physical examination, blood chemistry and haematology, urinalysis, electrocardiogram (ECG) and assessment of the minimal erythema dose (MED) for ultraviolet B (UVB) light to assess eligibility. Subjects with a clinically significant known medical condition, in particular any existing condition that

would affect sensitivity to cold or pain were excluded. Subjects with Fitzpatrick skin type V or VI, widespread acne, tattoos or scarring on the back were excluded due to the inability to accurately assess MED. Also any subject, who was a regular user of any illicit drugs, had a history of drug abuse or a positive drug screen at screening was excluded. Smoking and the use of xanthine-containing products were not allowed during dosing days. Alcohol was not allowed at least 24 hours before each scheduled visit and during the stay in the research unit.

Study drugs

Paracetamol (1000 mg), Δ9-THC (10 mg), promethazine (50 mg) or placebo were given as a single dose. Paracetamol 1000 mg is within the labelled dose range in the European Union (EU) and has been shown to be effective in reducing various types of pain. The currently used formulation of Δ9-THC (Namisol®, Echo Pharmaceuticals) has been administered in multiple studies including healthy volunteers[23] and different patient populations.[3,54,57] Δ9-THC has potential side effects, but is generally considered well-tolerated, even in high dosages. Promethazine is a classic H1-antihistamine with some anticholinergic effects. Daily doses up to 150 mg are prescribed for the treatment of allergic rhinitis and motion sickness. Single doses up to 50 mg are prescribed to induce mild sedation.

Due to unequal formulations (Δ9-THC was formulated as an oral tablet, whereas paracetamol and promethazine were formulated as capsules), matched placebo tablets for each treatment were administered in a double-dummy fashion to maintain blinding of treatment for participants and researchers.

Pharmacodynamic assessments

Pain detection and tolerance thresholds were measured using a battery of evoked pain tasks, as described previously.[21,37-40] The test battery consists of an integrated range of pain tasks for measuring different modalities of pain. Assessments were conducted twice pre-dose (double baseline) and 0.5, 1, 2, 3, 4, 6, 8 and 10 hours post-dose by trained personnel. Each measurement round was performed in a fixed order and took approximately 30 minutes to complete. To eliminate the risk of tissue damage, all pain tasks had a maximum safety cut-off. The aim of the test battery is to assess as objectively as possible the levels of pain induced by different noxious mechanisms in human subjects. A training session was included as part of the screening examination to reduce learning effects during the study and exclude non-responders (*i.e.*, subjects who reach PDT at >80% of the maximum at any of the nociceptive tasks, excluding the heat pain task) or extreme responders (subjects indicating to be intolerable to any of the nociceptive tasks). All measurements were performed in a quiet room with ambient illumination. Per session, there was only one subject present in the same room. To reduce variability from affects associated with fear of pain, the subjects themselves were responsible for starting and ending each pain task.

The battery of evoked pain tasks consists of the following tasks for nociception: the electrical stimulation task, pressure stimulation task, thermal (heat) pain and the cold pressor tasks. Furthermore, the test battery includes a model for inflammatory pain, the UVB model and a paradigm to quantify Conditioned Pain Modulation (CPM), formerly known as Diffuse Noxious Inhibitory Control (DNIC).

For the electrical stimulation task, the pressure stimulation task and the cold pressor task, pain intensity was measured continuously (beginning from when the first stimulus was applied until the end of the test) using an electronic visual analogue scale (eVAS) scale ranging from 0 (no pain) to 100 (most intense pain tolerable). Equipment was programmed to cease giving stimuli if the recorded pain intensity reaches the maximum pain score (100) or when the maximum safety level was reached. For the abovementioned pain tasks, the pain detection threshold (PDT) (defined as eVAS score > 0), pain tolerance threshold (PTT) (defined as eVAS score of 100) and Area Under the Curve (AUC) or Area Above the Curve (AAC) (Cold Pressor only) were determined. Additionally, a post-test Visual Analogue Scale (VAS) score (anchored with no pain (0) and worst pain imaginable (100)) was performed to retrospectively assess the worst pain experienced during the pain task. For the thermal pain task (normal skin and UVB exposed skin) only the (average of triplicate) PDT was determined, since assessment of heat PTT is prone to inducing tissue damage. For all nociceptive tasks were a PTT is determined (all except thermal pain) the primary endpoint is the PTT. For the thermal pain tasks (normal skin and UVB exposed skin), the PDT is the primary endpoint of the measurement. However, since each parameter (PDT, PTT, AUC/AAC) provides information on different aspects of the nociceptive system and pain perception, all variables are taken into account.

In addition to the evoked pain tasks, subjective assessment of sedation and psychotomimetic effects were included as PD outcome measures. Visual analogue scales (VAS) as originally described by Norris[36] have often been used previously to quantify subjective effects of a variety of sedative agents.[14,36] A set of VAS scales assessing alertness, mood, and calmness (Bond and Lader)[9] were used for subjective assessment of sedation. The VAS allows the subjects to evaluate their current subjective states. Each VAS scale consists of 2 words representing

opposite feelings placed to the left and right of a horizontal line. The subject is asked to mark his/her current feelings. Subjective psychotomimetic (psychedelic) effects were evaluated using VAS Bowdle. This scale has been used extensively to quantify subjective psychotomimetic effects of psychoactive compounds, including ketamine.[10] Bowdle Psychotomimetic Effects Scores consist of thirteen visual analogue lines ranging from 0 ('not at all) to 100 ('extremely'),[58] addressing various (abnormal) states of mind.

Sample size and randomisation

Based on literature, PDT for the cold pressor assessment was used for the sample size calculation as this assessment has been shown sensitive to the effects of Δ9-THC in previous research.[12] For the cold PDT, a sample size of 24 subjects has 80% power to detect a difference in means of 35%, assuming a standard deviation of differences of 0.5, using a paired t-test with a 0.05 two-sided significance level. For the sample size calculation, placebo data from a previous study with the battery of pain tasks were used to determine variability.[40] The balanced Williams design randomization code was generated using SAS version 9.1.3 by a study-independent statistician.

Statistical analysis

To establish whether significant treatment effects could be detected on the PD outcome variables, variables were analysed with a mixed model analysis of variance with treatment, time, sex, treatment by time and treatment by sex as fixed factors and subject, subject by treatment and subject by time as random factors and the average baseline measurement as covariate. The Kenward-Roger approximation was used to estimate denominator degrees of freedom and model parameters were estimated using the restricted maximum likelihood method. The general treatment effect and specific contrasts were reported with the estimated difference and the 95% confidence interval, the least square mean estimates and the p-value. Graphs of the Least Squares Means estimates over time by treatment were presented with 95% confidence intervals as error bars. All calculations of the pharmacodynamic parameters were performed using SAS for Windows version 9.1.3 (SAS Institute Inc., Cary, NC, USA). The main SAS procedure that was used in the analysis was "PROC MIXED". No adjustments for multiple comparisons were employed. The contrasts for the relevant time periods based on the expected PK profiles of the compounds of 0-4 hours are presented.

RESULTS

A total of 25 subjects were randomized, of which 23 subjects completed study participation. Two (2) subjects withdrew consent to participate for personal reasons, one of which was replaced. A summary of the baseline demographics is provided in Table 1.

Pharmacodynamics

Time profiles of the pharmacodynamic responses on PTT for each pain task, except heat pain (Normal skin and UVB skin) for which PDT is displayed, are presented in Figure 1. This figure also includes a graphical presentation of CPM (Delta PTT for electrical pain). PTT and PDT measurements were log (ln) transformed before analysis, due to the log normal distribution of the data. The results are presented as % change from baseline over a 10 hour period. A detailed description of the results of the Least Square Means (LSMeans) analyses for each treatment as well as contrasts compared to placebo (0-4 hours) can be found in Table 2. The results of the LSMeans analyses for the primary endpoints (PTT) are summarized in Figure 2. Each spoke represents one of the pain tasks, resulting in an effect profile compared to placebo per treatment. Here, the dashed placebo line represents the value to which other treatment effects are normalized. A contrast distal from placebo indicates that the LSMeans PTT for that treatment is greater than placebo, proximal indicates a LSMeans PTT lower than placebo.

Furthermore, the results for the subjective scales for cognitive functioning and psychotomimetic symptoms are presented in Table 3. Paracetamol did not show a significant reduction in pain sensation compared to placebo. A small increase in AUC (p=0.0314) was observed for the pressure pain task, indicating a slight increase in perceived pain sensation. Treatment with paracetamol did not lead to any observable changes in subjective cognitive functioning or mood. Promethazine demonstrated a statistically significant reduction in PTT for the cold pressor pain task (p=0.0189) and for the pressure stimulation task (p=0.0149), as well as an increase in AUC (p=0.0032), indicating an increase in pain sensation. In addition to the pharmacodynamic effects of promethazine on the pain task battery, a reduction in subjective alertness (p=0.0002) was observed. Δ9-THC did not show a statistically significant analgesic effect on any of the pain tasks. For the electrical stimulation task, the PTT was significantly decreased by -12.7%, (p=0.0134), also indicating an increase in pain sensation.

Furthermore, a significant reduction was observed for the pressure stimulation task PTT (p=0.0126) and AUC (p=0.0001). In addition to the effects observed on the pain task battery, Δ9-THC also demonstrated other pharmacodynamic effects, including a reduction on the composite scale for alertness (p=<.0001) and an increase on the composite scale for calmness (p=<.0001) compared to placebo. Moreover, significant psychotomimetic effects were observed expressed in changes in internal perception (p=<.0001) and external perception (p=<.0001), measured using the VAS Bowdle, as well as VAS Feeling high (p=<.0001). Of note, psychotomimetic effects were virtually absent after placebo treatment, thereby leading to high significance levels even at small effect sizes.

Safety

During the execution of this study, a total of 79 Treatment Emergent Adverse Events (TEAE) were registered. The majority (N=43, 54%) of these were recorded after treatment with Δ9-THC, after which 20 out of 25 subjects reported any event. Out of all TEAE, seven (8.8%) were considered moderate, all others were deemed mild. For Δ9-THC treatment, 60% of subjects reported an adverse event in the System Organ Class (SOC) Nervous system disorders, most of which were dizziness (40%) and headache (20%). Furthermore, 3 subjects (12%) reported euphoric mood and 3 subjects (12%) mild auditory hallucinations. A total of four subjects experienced TEAE of moderate intensity after treatment with Δ9-THC, leading to one or more missing measurement. For treatment with promethazine, most prominently somnolence (N=7, 30.4%) and fatigue (N=6, 26.1%) were observed. For paracetamol treatment, a total of six events were recorded, which is comparable to placebo treatment.

To investigate whether adverse events may have impacted the outcome of the pain tasks, a subgroup analysis was performed in which the 4 subjects that experienced at least one adverse event of moderate intensity were omitted from the analyses, as a moderate adverse event may have impacted pain tasks adjacent to its occurrence. This analysis had no significant impact on the interpretation of the results, therefore it was decided to report the results on the intention-to-treat (ITT) population.

DISCUSSION

The main objective of the present study was to investigate the effects of a classical (paracetamol) and a non-classical (Δ9-THC) analgesic on a battery of pain tasks (PainCart®), compared to placebo and a negative control (promethazine). The effects of the different treatment effects on each pain task are summarized in Figure 2, demonstrating the differential effect profile of each compound for the different pain tasks. Contrary to our expectation we found that paracetamol was not effective at reducing any of the pain modalities measured using the battery of evoked pain tasks. Furthermore, Δ9-THC did not show any acute analgesic effect, and even showed a hyperalgesic effect on two of five pain tasks, namely electrical and pressure pain. Finally, the negative control promethazine showed an increase in pain sensation for cold, pressure and inflammatory pain. In addition to the pain tasks, cognitive tests were performed to assess subjective alertness, mood, and psychotomimetic symptoms, which were moderately affected by treatment with Δ9-THC (alertness, calmness, internal and external perception) or promethazine (alertness).

This study did not demonstrate and acute analgesic effect of Δ9-THC, even though the subjective psycho-active effects were clearly present. As such we can conclude that the subjective psycho-active effects are not responsible for producing nociceptive analgesia. Moreover, the present study helped to further elucidate the mechanism of action of paracetamol as our results enable comparison to other analgesics with known mechanisms of action. Finally, when combining the findings of the current study with the existing body of evidence from this battery of evoked pain tasks, we have shown this battery to be a robust tool to determine analgesic effects that are specific, and thus not merely expressing sedation, otherwise the observed subjective sedation would have resulted in analgesia. This is an important finding for future studies in order to benchmark the effects of novel analgesics that may demonstrate a degree of sedation, including subtype selective $GABA_A$ agonists or novel mixed MOP/NOP receptor agonists.

At first glance it may have been surprising that the battery of evoked pain tasks was not sensitive to detect analgesic effects of paracetamol over a period of 4 hours post-dose, as it is among the most widely used analgesics worldwide. It has been shown to be effective in the treatment of different types of clinical pain, Although not all. While it is effective at reducing postoperative pain,[30,60] episodic tension headache[51] and acute migraine,[15] there is no evidence for its effectiveness in treating lower back pain[50,61] or pain related to osteoarthritis.[29] However, when looking at available literature on human evoked pain tasks in healthy volunteers, the image becomes more diffuse. For each of the pain tasks that were investigated in more than one clinical trial, positive as well as negative results have been reported: mixed results were obtained using the Cold pressor,[31,32,52,64] there was a single negative study for contact heat,[52] and again mixed results for

electrical pain,[5,16,41,52] mixed results for pressure pain[41,43,47] and only a single study showing analgesic effects on inflammatory pain using the UVB model.[42] Interestingly, the published studies measuring pain experience (post-test NRS or post-test VAS) tend to be more likely to show analgesia by paracetamol than studies measuring the more objective pain thresholds. This may indicate that paracetamol exerts its analgesic effect on the aspect of subjective pain experience by means of pain modulation rather than exerting changes in nociceptive pain perception thresholds. This differential effect was not observed in the present study. Additionally, the analgesic effects of paracetamol in human evoked pain models tend to be more subtle than the effect sizes that were used for the power calculation, therefore the study may have been underpowered. This applies specifically to for the Cold pressor task, where a non-significant increase in pain thresholds was observed. Summarising, based on the findings in literature and the aforementioned hypothesis, the outcome might have been different if a two-way crossover compared to placebo design was used in which different endpoints, *i.e.*, Laser Evoked Potentials,[4,34,35] were investigated.

Medicinal use of cannabis dates back tens of thousands of years.[1] In the last decade the role for (plant-derived or synthetic) cannabinoids has shifted from complementary medicine to regular care for pain related to oncology[2] and neuropathic pain resulting to spinal cord injury[62] or Multiple Sclerosis (MS).[49,53] The oral formulation of Δ9-THC (Namisol®) that was used in the current study has been shown to be effective in reducing neuropathic pain in a recently performed study in 24 patients suffering from progressive MS after 4 weeks of chronic treatment.[57] However, given its interaction with the endocannabinoid system it cannot be considered an "antinociceptive" analgesic, even if it may have analgesic effects in some conditions. This is reflected in the results of clinical studies using human evoked pain models to investigate pharmacology and mechanism of action. Only two studies investigating the effects of either inhaled cannabis or oral Δ9-THC showed a statistically significant reduction in pain sensation on the cold pressor task[12] or the heat pain task.[20] Two other studies investigating the effects on heat pain alone, did not demonstrate this improvement.[45,46] The results of the present study are in line with the results of Naef et al.[33] and Kraft et al.[25] who showed lack of analgesia on a set of pain tasks and even a significant or non-significant increase in pain sensation for electrical pain and cold pressor. The finding of Δ9-THC induced hyperalgesia has also been observed in the clinic.[6] A possible explanation is that this effect is dose-related, due to a bell-shaped effect curve. As proposed by Walter et al.,[59] this narrow therapeutic window may be the result of co-activation of TRPA1 and TRPV1 channels along with CB1 receptors by Δ9-THC at higher concentrations. The dose of 10 mg of the oral formulation of Δ9-THC was the highest single dose that is administered to healthy volunteers of this formulation to date.[23] Due to inter-subject variability this dose may have been too high for some, as in four subjects pharmacodynamic assessments were delayed or omitted as a result of adverse events associated with subjective effects and nausea. However, on a group level only a reasonable reduction in subjective alertness was reported. Furthermore, a post-hoc analysis excluding the measurements that may have been affected by AEs of moderate intensity did not lead to a different interpretation of the results compared to the ITT analysis. Therefore the ITT analysis was maintained and reported here. On the other hand, it is known that chronic and even acute exposure to Δ9-THC can induce a "transient amotivational state",[26] which may be misinterpreted as an apparent hyperalgesic state. This hyperalgesic state is in fact the result of the psychotropic effect profile of Δ9-THC, as subjects become less motivated to complete the pain tasks. Despite our efforts, human evoked pain tasks remain also sensitive to the affective components of pain sensation, and thus susceptible to detect changes in motivation as well as pure analgesia.

Over the recent years some evidence has gathered for the effectiveness of antihistaminergic drugs as adjuvant in the treatment of various pain states.[7,17,18] However, there is no evidence for any acute analgesic effect in humans. As such, promethazine (50 mg) was selected as a negative control for Δ9-THC and to investigate the effects of sedation on the battery of evoked pain tasks. In addition to an increased sensitivity for electrical and pressure pain, a decreased pain detection threshold for inflammatory pain was observed. Even though histamine is involved in the initial phase of erythema development, this role is not prominent in the delayed erythemic response[63] and as such administration 24 hours after UVB exposure is not likely to have influenced the pathophysiology of the UVB induced erythema. Thus, the results of promethazine treatment may indicate a reduction of pain endurance, which could result from reduced motivation associated with sedative effects (expressed as a reduction in subjective alertness), rather than suppositious analgesia resulting from delayed or impaired responsiveness.

The present study adds to a body of research studies in which this exact battery of evoked pain tasks was used to investigate various analgesic compounds alone[38-40] or combined.[37] As such, the battery of evoked pain tasks is pharmacologically validated for the effects of cannabinoids and sedatives. The battery of evoked pain tasks was not sensitive to detect analgesic effects of paracetamol, but that finding by itself provides information on the much debated and yet unrevealed pharmacological mechanism of action, as we are able to compare the

results to other compounds with known mechanism of action. As recognized before,[27,28,57] translatability of findings from human evoked pain models to clinical pain remains elusive. Nonetheless, if used prudently, this battery of pain tasks can provide invaluable information on pharmacodynamic and pharmacokinetic relationships in the early phases of drug development, especially when combined with other neurocognitive assessments.

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Table 1 – Summary demographic and baseline characteristics for all subjects (N=25)

AGE (YEARS)		
	Mean (SD)	24.0 (5.6)
	Median	23
	Min, Max	18, 45
BMI (KG/M^2)		
	Mean (SD)	23.5 (2.9)
	Median	23.7
	Min, Max	18.2, 29
SEX (N)		
	Female (%)	12 (48%)
	Male (%)	13 (52%)
RACE		
	Other	1 (4%)
	White	24 (96%)
FITZPATRICK SKIN TYPE		
	II: Always burns & tans min	6 (24%)
	III: Burns moderate & tan grad	11 (44%)
	IV: Burns minimal & tans well	8 (32%)
MED (MJ/CM)		
	Mean (SD)	777 (249)
	Median	702
	Min, Max	351, 1321

BMI = Body Mass Index; MED = Minimal Erythema Dose.

Table 2 – Summary of LSMeans analyses for battery of evoked pain tasks.

Endpoint	Placebo	Paracetamol		Promethazine		Δ9-THC	
	LSMean (95%CI)	LSMean (95%CI)	Contrast vs. placebo* (95%CI)	LSMean (95%CI)	Contrast vs. placebo (95%CI)	LSMean (95%CI)	Contrast vs. placebo (95%CI)
COLD PRESSOR (S)							
PTT	13.4 (12.5-14.3)	13.9 (13-14.8)	5.2% (-4.6%, 16.0%) p=0.3090	12.1 (11.3-13)	**-11.1% (-19.3%, -1.9%) p=0.0189**	13 (12.2-13.9)	2.5% (-7.0%, 12.9%) p=0.6183
PDT	3.2 (2.5-4)	3.3 (2.6-4.1)	3.5% (-15.0%, 26.0%) p=0.7292	2.7 (2.2-3.5)	-17.0% (-31.8%, 1.2%) p=0.0648	3.1 (2.5-4)	-0.8% (-18.5%, 20.7%) p=0.9335
AAC	860 (803-922)	902 (841-968)	7.8% (-3.8%, 20.9%) p=0.1938	780 (727-837)	-10.6% (-20.2%, 0.2%) p=0.0548	845 (789- 905)	4.1% (-7.0%, 16.6%) p=0.4806
VAS	56.9 (52.8-61)	58.3 (54.2-62.4)	2.59 (-0.45, 5.63) p=0.0940	58.4 (54.3-62.5)	1.48 (-1.56, 4.52) p=0.3366	57.6 (53.5-61.8)	0.11 (-2.93, 3.15) p=0.9444
ELECTRICAL STIMULATION (MA)							
PTT	22.1 (20.3-24.1)	19.7 (18.1-21.6)	-8.7% (-18.2%, 1.9%) p=0.1023	20.5 (18.8-22.4)	-7.7% (-17.2%, 3.0%) p=0.1495	20.1 (18.4-21.9)	**-12.7% (-21.5%, -2.8%) p=0.0134**
PDT	9.43 (8.44-10.53)	8.13 (7.27-9.1)	-9.9% (-22.8%, 5.3%) p=0.1896	8.95 (8-10.01)	0.8% (-13.7%, 17.8%) p=0.9211	9.19 (8.22-10.26)	-2.7% (-16.6%, 13.4%) p=0.7222
AUC	3244 (3112-3376)	3438 (3302-3573)	171.37 (-21.12, 363.87) p=0.0805	3324 (3189-3460)	76.86 (-115.81, 269.53) p=0.4311	3379 (3246-3512)	196.58 (6.98, 386.19) p=0.0423
VAS	54.6 (51.8-57.4)	56 (53.1-58.8)	1.71 (-1.18, 4.61) p=0.2414	52.5 (49.6-55.4)	-1.38 (-4.28, 1.52) p=0.3467	54.3 (51.4-57.1)	-0.68 (-3.53, 2.17) p=0.6372
CPM: ELECTRICAL STIMULATION (DIFFERENCE PRE-POST COLD PRESSOR) (MA)							
PTT	1.07 (0.64-1.51)	1.00 (0.56-1.45)	0.101 (-0.772, 0.973) p=0.8206	0.85 (0.41-1.29)	-0.186 (-1.050, 0.678) p=0.6716	0.77 (0.32-1.23)	0.099 (-0.785, 0.983) p=0.8254

Table 2 – continued

PDT	1.07 (0.64-1.51)	1.00 (0.56-1.45)	0.678 (-0.566, 1.921) p=0.2841	0.85 (0.41-1.29)	0.052 (-1.186, 1.290) p=0.9339	0.77 (0.32-1.23)	-0.144 (-1.398, 1.109) p=0.8206
AUC	-147 (-192--102)	-113 (-159--67)	-24.74 (-107.64, 58.17) p=0.5574	-108 (-154--61)	13.44 (-69.10, 95.98) p=0.7488	-79 (-125--33)	9.63 (-73.60, 92.87) p=0.8200
VAS							
PRESSURE STIMULATION (KPA)							
PTT	39.9 (36.3-43.9)	38.9 (35.3-42.8)	-5.1% (-11.9%, 2.2%) p=0.1653	37.1 (33.7-40.8)	**-8.9% (-15.4%, -1.8%) p=0.0149**	36.5 (33.1-40.1)	**-9.0% (-15.6%, -2.0%) p=0.0126**
PDT	16.7 (14.2-19.6)	15.5 (13.2-18.2)	-8.5% (-19.1%, 3.5%) p=0.1552	14.8 (12.6-17.4)	-7.1% (-17.8%, 5.1%) p=0.2392	14.3 (12.2-16.8)	-9.9% (-20.3%, 1.9%) p=0.0972
AUC	6761 (6457-7064)	6906 (6601-7211)	**248.01 (22.33, 473.69) p=0.0314**	7072 (6767-7377)	**341.93 (115.96, 567.89) p=0.0032**	7180 (6876-7484)	**446.38 (221.09, 671.67) p=0.0001**
VAS	50.2 (44.2-56.2)	51.4 (45.4-57.4)	1.12 (-1.60, 3.85) p=0.4176	50.3 (44.2-56.3)	-0.20 (-2.92, 2.52) p=0.8841	50.4 (44.4-56.5)	0.35 (-2.35, 3.06) p=0.7964
NORMAL HEAT (°C)							
PDT	45.1 (44.7-45.6)	45.5 (45-46)	0.5% (-0.9%, 2.0%) p=0.4434	45 (44.6-45.5)	-0.6% (-2.0%, 0.8%) p=0.3830	45.3 (44.8-45.8)	0.3% (-1.1%, 1.7%) p=0.7229
UVB HEAT (°C)							
PDT	39.7 (39.1-40.2)	39.8 (39.3-40.3)	0.2% (-1.1%, 1.4%) p=0.8033	38.8 (38.3-39.3)	**-2.8% (-4.1%, -1.6%) p=<.0001**	39.4 (38.9-40)	-1.0% (-2.3%, 0.3%) p=0.1220

PTT = Pain Tolerance Threshold; PDT = Pain Detection Threshold; AAC = Area Above the Curve; AUC = Area Under the Curve; VAS = Visual Analogue Scale; CPM = Conditioned Pain Modulation/ * Contrasts over 0-4 hours post dose.

Table 3 – Summary of LSMeans analyses for subjective cognitive functioning and psychotomimetic symptoms.

	Placebo	Paracetamol		Promethazine		Δ9-THC	
	LSMean (95%CI)	**LSMean (95%CI)**	**Contrast vs. placebo* (95%CI)**	**LSMean (95%CI)**	**Contrast vs. placebo (95%CI)**	**LSMean (95%CI)**	**Contrast vs. placebo (95%CI)**
VAS BOND & LADER							
Alertness (mm)	49.7 (48.7-50.7)	49.8 (48.8-50.8)	0.07 (-1.55, 1.68) p=0.9339	47.2 (46.2-48.2)	**-3.11 (-4.75, -1.48) p=0.0002**	45.7 (44.7-46.7)	**-5.83 (-7.45, -4.21) p=<.0001**
Calmness (mm)	51.6 (50.6-52.6)	51.1 (50-52.1)	-0.73 (-2.57, 1.12) p=0.4369	51.9 (50.9-53)	0.46 (-1.38, 2.30) p=0.6236	53.6 (52.6-54.7)	**3.97 (2.11, 5.82) p=<.0001**
Mood (mm)	50.4 (49.7-51.1)	50.2 (49.5-50.9)	-0.42 (-1.39, 0.55) p=0.3914	50.7 (50-51.4)	0.10 (-0.88, 1.07) p=0.8408	51 (50.3-51.6)	0.76 (-0.21, 1.74) p=0.1244
VAS BOWDLE							
Feeling High (LOGmm)	0.33 (0.28-0.39)	0.31 (0.26-0.37)	-0.0295 (-0.1347, 0.0757) p=0.5804	0.35 (0.29-0.4)	0.0189 (-0.0859, 0.1237) p=0.7225	0.71 (0.65-0.77)	**0.7232 (0.6164, 0.8300) p=<.0001**
Internal perception (LOGmm)	0.32 (0.29-0.34)	0.31 (0.29-0.34)	-0.0061 (-0.0470, 0.0348) p=0.7677	0.33 (0.31-0.35)	0.0269 (-0.0139, 0.0678) p=0.1951	0.4 (0.38-0.42)	**0.1705 (0.1292, 0.2117) p=<.0001**
External perception (LOGmm)	0.33 (0.28-0.37)	0.32 (0.27-0.36)	-0.0143 (-0.0957, 0.0670) p=0.7279	0.34 (0.29-0.39)	0.0148 (-0.0664, 0.0960) p=0.7189	0.55 (0.5-0.59)	**0.4289 (0.3466, 0.5112) p=<.0001**

VAS = Visual Analogue Scale; * Contrasts over 0-4 hours post dose / Bold values signify that the p-value <0.05

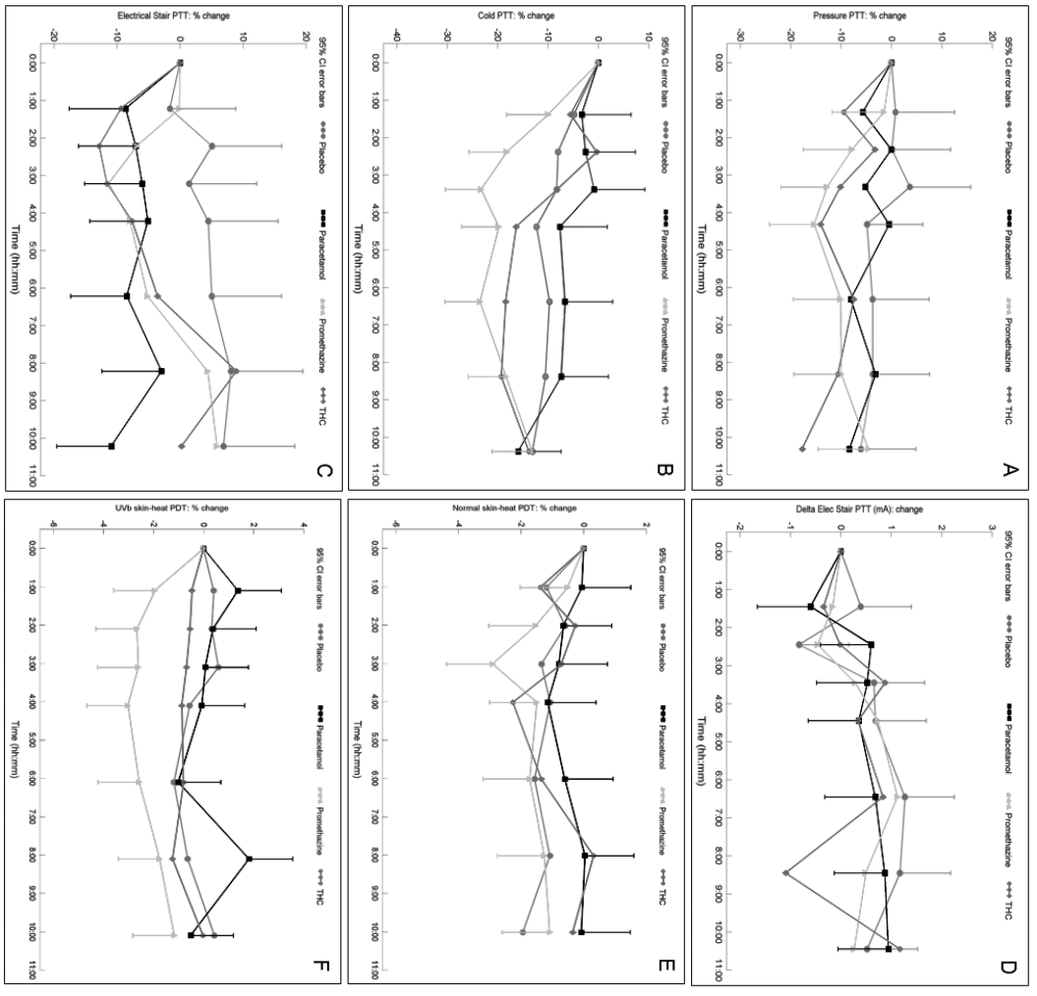

Figure 1 – Overview of Change from Baseline time profiles for battery of evoked pain tasks.

Panel A = Pressure pain task in KPA (PTT); Panel B = Cold pressor in S (PTT); Panel C = Electrical pain task in MA (PTT); Panel D = Conditioned Pain Modulation (CPM) in delta MA (PTT) Panel E = Thermal pain normal skin in °C (PDT); Panel F = Thermal pain UVB skin in °C (PDT) / Lines with Circles (●) = placebo; lines with squares (■) = paracetamol; lines with triangles (▲) = promethazine; lines with diamonds (♦) = Δ9-THC / PTT = Pain Tolerance Threshold; PDT = Pain Detection Threshold.

Figure 2 – Spider plot overview of Pharmacodynamic response profile for battery of evoked pain tasks normalized to placebo (0-4 hours. Dashed placebo line represents the value to which other treatment effects are normalized. Distal from placebo indicates Least Square Mean PTT greater than placebo, proximal indicates Least Square mean PTT lower than placebo. Actual values are described in Table 2. A star (*) indicates a statistically significant (P<0.05) difference compared to placebo for treatment on pain task.