International Association for Cannabis as Medicine

In cooperation with the Berlin Medical Association and the Charité

2001 Congress
on Cannabis and the Cannabinoids

26-27 October 2001
Berlin
Charité – Virchow Campus

Program and Abstracts

International Association for Cannabis as Medicine

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2001 Congress on Cannabis and the Cannabinoids

Place	Charité, Virchow Clinic (Virchow Klinikum) Mittelallee 3, 2nd Floor, 13344 Berlin
Registration Fee	50 DM (German Marks) a day 100 DM whole congress Free for members of the IACM
Organizer	IACM Arnimstraße 1 A, 50825 Köln Phone: 49-(0)221-95439229 Fax: 49-(0)221-1300591 E-mail: info@cannabis-med.org Internet: http://www.cannabis-med.org
Cooperation Partners	Berlin Medical Association Charité
Program Committee	Franjo Grotenhermen Gernot Ernst Martin Schnelle Kirsten Müller-Vahl
Supporters	Deutsche AIDS-Hilfe Schmerztherapeutisches Kolloquium German Society for Addiction Medicine

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Program - 26 October 2001

0800-0900 Registration

0900 - 1230: Lectures

0900 **Greetings**
Raphael Mechoulam (IACM)
Konrad Falke (Charité)

0915-1045 **First Session** Chair: Rudolf Brenneisen, Ethan Russo

0915 Richard E. Musty: Effects of a cannabis extract in animal tests of depression, spasticity and antinoception: a preliminary report

0930 Jens A. Wagner: Endocannabinoid activation in cardiogenic shock and the advanced state of liver cirrhosis and cannabinoid effects on local and systemic hemodynamics in vivo

0945 Margret R. Höhe: Comparative sequencing of the human CB1 can nabinoid receptor gene coding exon: no structural mutations in individuals exhibiting extreme responses to cannabis

1000 Bela Szabo: Presynaptic inhibition of neurotransmission in nuclei belonging to the extrapyramidal motor control system

1015 Jörg Fachner: Temporal, occipital and parietal EEG changes in pre/post-THC-music and -rest

1030 Raphael Mechoulam: Endocannabinoids as neuroprotective agents

1045 - 1115 **Coffee Break**

1115-1230 **Second Session** Chair: Bela Szabo, Hartmut Hagmeister

1115 Ester Fride: Endogenous cannabinoids: critical role in food ingestion in the newborn

1130 Donald I. Abrams: Short-term effects of cannabinoids in patients with HIV infection

1145 Karen J Berkley: Influence of synthetic cannabinoid ligands on the rat bladder and uterus: clinical implications

1200 Ciaran M Brady: Acute and chronic effects of cannabis based medicinal extract on refractory lower urinary tract dysfunction in patients with advanced multiple sclerosis - early results

1215 Ulrike Hagenbach: Clinical pilot study of delta-9-tetrahydrocannabinol (THC) as an alternative therapy for overactive bladders in spinal cord injury patients

1230 Andreas M. Stadelmann: Alteration of cognitive functioning of the frontal cortex by 9-tetrahydrocannabinol in humans

1230 - 1400 **Lunch**

1400-1800: Workshops

Two workshop parallel

1400-1530 **Sepsis/circulation**
with Bela Szabo, Didier Keh, Eberhard Schlicker, and Jens Wagner

1400-1530 **Politics**
with Myra Klee, Franjo Grotenhermen, Ricardo Navarrete-Varo, Ethan Russo, et al.

1530-1600 **Coffee Break**

1600-1800 **Appetite loss/nausea/antiemesis**
with Donald Abrams, Ester Fride, Martin Schnelle, Winfried Meissner, and Florian Strasser

1600-1800 **Dependency/addiction**
with Thomas M. Tzschentke, Tod Mikuriya, Derik Hermann, and Hans-Günter Meyer-Thompson

18.00 **End of the session**

Program - 27 October 2001

1400 - 1530: Lectures

Chair: Richard Musty, Ulrike Hagenbach

1400	Kirsten Müller-Vahl: Cannabinoids in the treatment of Tourette-syndrome
1415	William Notcutt: Medicinal cannabis extracts in chronic pain: Comparison of two patients with multiple sclerosis
1430	Claude Vaney: A clinical study with a standardized cannabis extract in multiple sclerosis
1445	Rudolf Brenneisen: The analgesic effect of oral THC alone or in combination with morphine in healthy subjects under experimental pain conditions
1500	William Notcutt: Medicinal cannabis extracts in chronic pain: Comparison of two patients with back pain and sciatica
1515	Clare Hodges: Information gained from current medicinal users of cannabis for multiple sclersois

1530 - 1600 **Coffee Break**

1600-1800: Workshops

Two workshops parallel

1600-1800 **Pain**
with Anita Holdcroft, Rudolf Brenneisen, Raphael Mechoulam, William Notcutt, Gernot Ernst, and Karen Berkley
Poster session within the Pain Workshop

1600-1800 **Neurology**
with Rik Musty, Kirsten Müller-Vahl, Claude Vaney, Ciaran Brady, and Ulrike Hagenbach

1800 **End of the conference**

cannabis medicine International Association for Cannabis as Medicine

GREETINGS BY FRANJO GROTENHERMEN

Cannabis and single substances that influence the endogenous cannabinoid system have a remarkable broad therapeutic potential. Several effects that are not mediated by cannabinoid receptors or by unknown mechanisms have come into focus as well. Some people show greater sympathy for natural products, others for synthetic derivatives. Both show promising results in recent clinical studies and are supposed to find their place in modern medicine. Further research will show which hopes will be fulfilled. We observe an increasing factual discussion on medicinal effects and unwanted side effects of cannabinoids by scientists, physicians, the public and politicians. This will ease research and increase our knowledge.

Our aim as scientists and clinicians is to improve the health and quality of life of patients with serious, mostly chronic, often life threatening diseases. I am pleased to notice the interest in this first international meeting of a young medical society. I am happy about the support by the Charité and the Berlin Medical Association. I happy about additional generous support with financial means, ideas and concrete help by other institutions and persons. And as you I am full of expectations with regard to the lectures, workshops, exchange of experience and impressions. I wish you some inspired days in Berlin!

Dr. med. Franjo Grotenhermen
Chairman
International Association for Cannabis as Medicine

GREETINGS BY KONRAD FALKE

Cannabis as therapeutic drug has a long tradition in human history. Newer drugs and its possible misuse lead to stagnation in clinical cannabis research until today. Since we learned about the endogenous cannabinoid system as crucial part of the human neurobiology we approach today a new phase of cannabis research beyond positive and negative prejudices. As anaesthesiologists we are particularly interested in the involvement of cannabinoids in the mechanisms of hypovolemic shock and sepsis or in the possible therapeutic option to treat special features of chronic pain syndromes as coanalgetic. But also new insights in the cannabinoid pharmacology of gastroenterologic syndromes or their interaction with neurobiological processes might give new challenging possibilities for understanding, diagnosis and treatment of various diseases. I am therefore very happy to welcome the participants of the congress „Cannabis and cannabinoids as medicine“ and wish inspiring discussions. If Berlin can contribute to new insights and new projects in this field, we reached the goal of this meeting.

Professor Dr. med. Konrad Falke
Director, Clinic for Anaesthesiology and Intensive Care Medicine
Charité Campus Virchow Clinic

EFFECTS OF A CANNABIS EXTRACT IN ANIMAL TESTS OF DEPRESSION, SPASTICITY AND ANTINOCICEPTION: A PRELIMINARY REPORT

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The effects of an extract of cannabis (GW Pharmaceuticals) in animal tests of depression, spasticity and antinociception were examined. The extract contained □9 tetrahydrocannabinol (THC) and no other cannabinoids. The extract was administered in doses of 0, 0.5 and 1.0, 2.0 and 4.0 and 4.0, 8.0 mg/kg (i.p. in Tween-80 saline) by weight of THC in the extract in all experiments.

DEPRESSION. Cannabinoids have been thought to relieve depression, but it is unclear whether or not these observations are due to agonist or antagonist effects on the CB_1 receptor. Experiments were conducted to determine whether or not the specific antagonist SR141716 or the THC extract would act like an antidepressant in the tail suspension test, which is a valid screening test for known antidepressants. The subjects were naïve male and female C57Bl6 inbred mice (Jackson Laboratories). Each mouse was suspended by applying adhesive tape near the end of the tail, with a hook between the tape and the tail. After several attempts mice show increasing periods of immobility (giving up escape attempts). Groups of mice were tested in the following drug conditions: vehicle control, 0.1, 0.5, 1.0, 2.0, and 4.0 mg/kg i.p. Movements increased a function of dose. Statistical significance was found at 1.0, 2.0, and 4.0 mg/kg doses. The cannabis extract did not produce an anti-depressive effect. Thus, we hypothesize that antagonists of the CB_1 receptor, including the natural cannabinoid, cannabidiol (CBD) may decrease symptoms of depression. Tests of a cannabis extract high in CBD are underway.

SPASTICITY. Patients with multiple sclerosis or spinal cord injury report reduced spasticity associated with their use of cannabis in a self report questionnaire. Both synthetic THC and cannnabidiol have been reported to reduce spasticity in mutant rodents with inherited 2spasticity. Experiments were conducted using C57-GLRB^{spa} mice, which have an autosomal recessive gene for spasticity. On average, 25% of the offspring develop spasticity, characterized by reduced righting reflex, spastic clasping of the hind paws when suspended by the tail, and spontaneous jumping. These behaviors were videotaped and scored by a rater blind to the drug doses. Durations of the righting reflex were recorded using a computerized timer. Frequencies of other behaviors were counted. The THC extract produced a decrease in spastic behaviors. This is the first report of an anti-spasmodic effect of a high THC extract.

Antinociception. Tail Flick tests were conducted by placing C57 mice in a restraining tube, with the tail extended from the end of the tube. The tail was placed in a water bath at a constant temperature of 55° C. A metal collar was placed on the base of the tail which was connected to computerized timer which detected the latency of the tail flick from the water. Latencies to withdraw the tail were reduced in a dose dependent manner after administration of the extract. These data suggest that THC extracts will be useful for spastic conditions and for pain.

Acknowledgements: The authors thank GW Pharmaceuticals and Sanofi-Synthelabo for their support.

ENDOCANNABINOID ACTIVATION IN CARDIOGENIC SHOCK AND THE ADVANCED STATE OF LIVER CIRRHOSIS AND CANNABINOID EFFECTS ON LOCAL AND SYSTEMIC HEMODYNAMICS *IN VIVO*

Jens A. Wagner

Medizinische Universitätsklinik Würzburg

In experimental animals, the most prominent cardiovascular effects of cannabinoids are prolonged hypotension and bradycardia. Under certain pathological situations, e.g. hemorrhagic or septic shock, endocannabinoids contribute to low blood pressure via activated peripheral CB1 receptors.

Results from three recent studies from our laboratory are presented below.

1) Hypotension and cardiogenic shock are common complications in acute myocardial infarction. In a rat model of left coronary artery ligation to produce myocardial infarction, cannabinoids generated from monocytes and platelets contribute to hypotension in cardiogenic shock. CB1-blockade restores blood pressure but increases early-mortality, possibly by impairing endothelial function.

2) Using the radioactive microsphere technique, we examined the effects of various cannabinoids on systemic hemodynamics. In brief, cannabinoids elicit profound coronary and cerebral vasodilation *in vivo* by direct activation of vascular CB1 receptors. Anandamide decreases blood pressure by reducing systemic vascular resistance, leaving cardiac output and stroke volume unchanged. In contrast, the potent synthetic CB1 agonist HU-210 decreases cardiac output without significantly affecting systemic vascular resistance. Autoregulation, a decrease in sympathetic tone or active breakdown metabolites are not likely for the effects seen.

3) Patients and rats with liver cirrhosis have low blood pressure, which in case of the latter, can be elevated by the CB1 receptor antagonist SR141716A, which also reduces the elevated mesenteric blood flow and portal pressure. Monocytes from cirrhotic but not control patients or rats elict SR141617A-sensitive hypotension in normal recipient rats and showed significantly elevated levels of anandamide. Compared with non-cirrhotic controls, in cirrhotic human livers there was a three-fold increase in CB1 receptors on isolated vascular endothelial cells. The results implicate anandamide and vascular CB1 receptors in the vasodilated state of advanced liver cirrhosis and indicate a novel approach for ist management.

COMPARATIVE SEQUENCING OF THE HUMAN CB1 CANNABINOID RECEPTOR GENE CODING EXON: NO STRUCTURAL MUTATIONS IN INDIVIDUALS EXHIBITING EXTREME RESPONSES TO CANNABIS

Margret R. Hoehe[1], Thomas Rinn[3], Christina Flachmeier[1], Petra Heere[1], Hanns J. Kunert[3], Bernd Timmermann[1,2], Karla Köpke[1,2] and Hannelore Ehrenreich[3]

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Rare but striking individual differences in responsiveness to cannabinoids have been observed that might involve mutations in the gene encoding the brain-expressed cannabinoid receptor. In a preliminary study, the human CB1 cannabinoid receptor coding region was comparatively sequenced in different groups of individuals: one group showed acute psychotic symptoms after cannabis intake, while another group did not develop any psychopathology after long-term heavy cannabis abuse. No evidence for structural mutations was obtained, which might provide some insight into the molecular basis of individually different responsiveness to cannabinoids. Comparison of CB1 cannabinoid receptor amino acid sequences between species substantiated evidence that the protein sequence is relatively well conserved.

PRESYNAPTIC INHIBITION OF NEUROTRANSMISSION IN NUCLEI BELONGING TO THE EXTRAPYRAMIDAL MOTOR CONTROL SYSTEM

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Introduction. The neuronal subtype of the cannabinoid receptors, the CB_1 cannabinoid receptor, is widely distributed in the brain. Impressive is the high density of CB_1 receptors in nuclei belonging to the extrapyramidal motor control system, i.e., corpus striatum, substantia nigra, globus pallidus and subthalamic nucleus. Our aim was to clarify the function of cannabinoid receptors in these nuclei.

Methods. Experiments were carried out on thin brain slices prepared from brains of rats and mice. The brain slices were superfused and the electrophysiological properties of the neurons were studied with the patch-clamp technique.

Results. We first studied the role of cannabinoid receptors in the corpus striatum (Szabo et al., 1998; Neuroscience 85:395-403). The principal neuron in the striatum, the medium spiny neuron, was patched. GABAergic synaptic transmission between parvalbumin-positive interneurons and medium spiny neurons was activated by electrical stimulation. The synthetic CB_1/CB_2 cannabinoid agonists WIN55212-2 and CP55940 decreased the amplitude of the recorded inhibitory postsynaptic currents (IPSCs). The effect of WIN55212-2 was prevented by the CB_1-selective antagonist SR141716A. We excluded interference of the cannabinoids with postsynaptic receptors on medium spiny neurons: WIN55212-2 did not influence the currents elicited by the $GABA_A$-receptor agonist muscimol. Thus, cannabinoids presynaptically inhibit GABAergic neurotransmission between parvalbumin-positive interneurons and medium spiny neurons.

In the next series of experiments, we clarified the function of the high number of CB_1 receptors which are localized on terminals of striato-nigral axons in the substantia nigra pars reticulata (SNR). SNR neurons were patched and IPSCs were elicited by electrical stimulation of the striato-nigral pathway in the corpus striatum. Activation of CB_1 receptors inhibited the IPSCs. Three observations indicate that the neurotransmission was inhibited with a presynaptic mechanism. (1) Cannabinoids did not influence currents elicited by direct activation of $GABA_A$-receptors on SNR neurons. (2) Cannabinoids enhanced the ratio of amplitudes of two IPSCs elicited by two pulses with an interstimulus interval of 100 ms (paired pulses). (3) Finally, cannabinoids did not change the amplitude of miniature IPSCs recorded in the presence of tetrodotoxin. Thus, cannabinoids presynaptically inhibit GABAergic neurotransmission between striato-nigral axons and SNR neurons.

We have also studied interference of cannabinoids with excitatory neurotransmission using the techniques described above. Activation of CB_1 receptors inhibited neurotransmission between glutamatergic axons arriving from the subthalamic nucleus and SNR neurons with a presynaptic mechanism (Szabo et al., Neuroscience 2000; 97: 89-97).

Finally, we analysed the effects of cannabinoids on dopamine release in the striatum from terminals of nigro-striatal axons (Szabo et al., J. Neurochem. 1999; 73:1084-1089). Dopamine release was elicited by applying single electrical pulses within the striatum and determined using fast cyclic voltammetry. Cannabinoids did not change dopamine release from terminals of nigro-striatal axons.

Conclusion. We identified the role of cannabinoid receptors in nuclei belonging to the extrapyramidal motor control system. Inhibitory and excitatory neurotransmission were inhibited as well, and the mechanism was presynaptic inhibition. Summarising our results and results described in the literature, it seems that presynaptic inhition of neurotransmission is the typical neuronal effect of cannabinoids. Cannabinoids can elicit a marked extrapyramidal motor disturbance, catalepsy. Inhibition of the GABAergic neurotransmission between striato-nigral axons and SNR neurons, as observed by us, could explain the catalepsy.

TEMPORAL, OCCIPITAL AND PARIETAL EEG CHANGES IN PRE/POST-THC-MUSIC AND –REST

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Cannabis is known to change auditory perception as many musicians and music listeners report in narratives, interviews and biographies. Listening abilities seem to be enhanced although audiological research on basic auditory processing didn't report significant changes. Topographic imaging studies on intensity and locality of cerebral processes investigating cannabis and auditory perception are not available. An ethnographic electrophysiological study with 4 healthy volunteers (3m/1f) was conducted in a habituated naturalistic setting. Pre/post-THC EEG-Brainmapping was performed while four subjects (non-musicians) in a comfortable armchair listened with closed eyes to one piece of instrumental music and two songs. Music was heard in a certain order before/after smoking Nepalese Hash (20 mg Δ^9 THC) in a tobacco joint. 28 channel EEG-Data were averaged and analysed with a T-Test and a visual topographic schedule. Individual (IA) and group average (GA) comparisons between Pre/Post-THC-Rest (PPTR), and Pre/Post–THC-Music (PPTM) were performed. One subject has been investigated with follow-up. A visual inspection of the IA maps showed intraindividual stable EEG Gestalts in rest and activation and confirmed known EEG sensitivity to personality and situation, even in the follow-up. Topographic changes spread interindividually. Listening to the first piece of instrumental music exhibited high significant changes ($p<0.001$) with three subjects after smoking but significance decreased in the sequence of music. One person showed a marked difference of cortical activation between songs and instrumental music. Compared to instrumental music, listening to songs desynchronised the EEG in the left rear hemisphere with an increase of β even in the follow - up. An analysis of GA Pre/Post-T-Test of the first music revealed the right parietal-occipital PO2-Electrode with a significant ($p<.01$) change. During Post-THC-Rest (PoTR) α-waves decreased; however, compared to Pre-THC-Rest (PrTR) and Pre-THC-Music (PrTM), the Post-THC-Music (PoTM) showed higher α-percentage and -power in the parietal cortex on four subjects, while other frequencies decreased in power. T-Test of PrTR and PoTM, further PPTM comparisons elicited a significant change ($p<0.025$) in left occipital area. Here, a transition to higher frequency in the PPTM spectrum was also observed. Comparing PPTM, differences ($p<0.025$) were also found in the right frontotemporal cortex on θ, and on α in the left occipital cortex. During PrTM listening θ-percentage increased but decreased more in PoTM than during rest. In both temporal lobes θ-amplitudes decreased during PoTM as well. Changes in temporal and occipital areas and increasing α-signal strength in parietal association cortex seem to represent an interindividual constant EEG correlate of altered music perception and hyperfocusing on the musical time-space. α-amplitude changes show a marked similarity to reverse α-findings in studies with gifted individuals. Jausovec concluded that an increase in α-percentage represented a more effective strategy in task-specific information processing. Cerebral change of perception seemed to be initially indicated throughout the significant spectrum change on the right parietal-occipital electrode, as well as allover changes of temporal and occipital areas, both involved in auditory perceptual changes. Changes in occipital areas might indicate an 'insight into the space beween the notes' mediated throughout desynchronisation in the visual association cortex. This area should be regarded in further investigations. Basic research on cannabis-induced auditory changes seems to be indicated to estimate possible benefits for the hearing impaired. Speech perception enhancement might be of interest for aphasia research.

ENDOGENOUS CANNABINOIDS: CRITICAL ROLE IN FOOD INGESTION IN THE NEWBORN

Ester Fride

Hebrew University of Jerusalem and the College of Judea and Samaria, Ariel.

Since the discovery of the first endogenous cannabinoid, anandamide, additional 'endocannabinoids' have been isolated. Thus far they all are fatty acid-derived ethanol amides ('anandamide'), esters (2-arachidonyl glycerol, '2-AG') or ethers ('noladine').
A multitude of physiological roles have been ascribed to the endocannabinoids. These include motor behavior, fertility and sexual behavior, anxiety, blood pressure, sleep and feeding and appetite.

Endocannabinoids have been detected in foodstuffs such as chocolate, soy beans and milk. We have shown that oral administration of high amounts of endocannabinoids has marijuana-like effects in mice. Hence it is possible that the presence of the endocannabinoids in chocolate explains at least part of the human addiction to chocolate.
It is well known that marijuana increases appetite. Since endocannabinoids have been detected in milk, we hypothesized that endocannabinoids may play a role in development of the newborn. Indeed, when we blocked cannabinoid receptors in newborn mice by administration of the cannabinoid-1 (CB1) receptor antagonist SR141716A. on the first day of life, the mouse pups did not gain weight and died within the first week after birth. Co-administration of the CB1 receptor agonist Δ^9-tetrahydrocannabinol almost completely reversed the devastating effects of blocking the CB1 receptors. Further, administering Cannabidiol, a nonpsychoactive cannabinoid, did not reverse SR141716A-induced growth stunting. Moreover, SR144528, the "peripheral" CB_2 receptor antagonist did not affect pup growth. Thus it appears that the growth-inhibiting effects of SR141716A are specifically mediated by CB_1 receptors.
Maternal behavior of the dams was <u>not</u> different towards SR141716A-treated newborns compared to controls. However, milkbands were detected only in 15% of the SR141716A-treated pups (compared to 100% in controls), indicating that the cannabinoid antagonist-induced pup mortality was mediated by an inability to ingest milk.
We conclude that the appetite-enhancing effects of marijuana in adults may only be the 'tip of the iceberg' of the critical role for newborn growth and survival of endogenous cannabinoid substances found in maternal milk.

SHORT-TERM EFFECTS OF CANNABINOIDS IN PATIENTS WITH HIV INFECTION

Donald I. Abrams, Roslyn J. Leiser, Joan F. Hilton, Starley B. Shade, Tarek A. Elbeik, Francesca A. Aweeka, Judith A. Aberg, Neal L. Benowitz, Barry M. Bredt, Steven G. Deeks, Bradley W. Kosel, Joseph M. McCune, Thomas F. Mitchell, Kathleen Mulligan, and Morris Schambelan.

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INTRODUCTION: Cannabinoid use could potentially alter HIV RNA levels by two mechanisms- immune modulation or through cannabinoid:protease inhibitor interactions as both share cytochrome p450 metabolic pathways. Widespread use of smoked marijuana in symptomatic HIV patients prompted this safety study.

METHODS: We conducted a randomized, placebo controlled 25-day inpatient study from May 1998 to May 2000. HIV positive subjects on a stable protease inhibitor regimen containing either indinavir or nelfinavir were randomized to receive three times daily before meals either a 3.95% tetrahydrocannabinol (THC) marijuana cigarette, oral dronabinol (delta-9-THC) 2.5 mg or oral placebo. HIV RNA levels were measured utilizing branched DNA assays. T lymphocyte subset and protease inhibitor and cannabinoid pharmacokinetic analyses were performed. Activity parameters included appetite, caloric intake, body weight and body composition.

RESULTS: 62 of the 67 randomized subjects were evaluable for the primary endpoint; 20 randomized to marijuana, 22 to dronabinol and 20 to placebo. Baseline HIV RNA level was <50 copies/mL for 37 (55%) and the median CD4+ cell count was 340/mm^3. Thirty subjects were on indinavir containing regimens; 37 were on nelfinavir. Overall there was no change in HIV RNA levels over the 21-day study period in any of the three treatment groups. Median CD4+ and CD8+ lymphocyte counts rose in all three groups, with significantly greater increases in CD8+ lymphocyte counts in the marijuana group relative to placebo recipients. No clinically significant interaction between smoked marijuana and protease inhibitor levels was detected. Statistically significant weight gain over baseline was seen in the marijuana (+3.0 kg, p=0.021) and dronabinol (+3.2 kg, p= 0.004) groups compared to placebo recipients (+1.1 kg). Weight gained was mostly fat as measured by dual-energy x-ray absorptiometry (DEXA) scan.

CONCLUSIONS: Controlled clinical trials investigating smoked marijuana can be conducted. Neither smoked nor oral cannabinoids have an adverse effect on HIV RNA levels, immune parameters or protease inhibitor kinetics over a 21 day treatment period in patients with HIV infection on a stable antiretroviral therapy regimen. Use of both smoked marijuana and dronabinol lead to increased weight gain compared to placebo. Further studies to investigate the therapeutic potential of smoked marijuana and other cannabinoids are warranted.

Supported by NIH grants 1RO1 DA/MH11607, 5-MO1-RR00083-38 and P30-MH59037

INFLUENCE OF SYNTHETIC CANNABINOID LIGANDS ON THE RAT BLADDER AND UTERUS: CLINICAL IMPLICATIONS

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INTRODUCTION AND METHODS: Cannabinoid CB1 receptors in rodent uterus and bladder (2,4,7,9) may be a target for synthetic ligands that could act differently in the two organs and in different clinically-relevant conditions. To begin testing these hypotheses, we examined how the synthetic high-affinity cannabinoid receptor agonist WIN 55,212-2 (WN2) acts on the bladder and uterus before and after either bladder inflammation or hypogastric neurectomy (HYPX). The influence of co-delivery of the CB1 receptor antagonist SR141716A (SR) was also tested. In urethane-anesthetized rats in one estrous stage (metestrus), the bladder was catheterized per urethra to measure micturition threshold (MT) via cystometry, and a flexible balloon put in the left uterine horn to measure uterine contractions. The left femoral artery was deeply catheterized for close-arterial injections of either vehicle (4µl DMSO in 0.2ml saline), or WN2 in 4 doses (0.01-1.0µmol/kg), or WN2 (0.5µmol/kg) mixed with SR (1.5µmol/kg), or SR alone (1.5µmol/kg). In some cases, ligands were delivered via the tail vein.

RESULTS AND CONCLUSIONS: WN2 dose-dependently increased MTs and the amplitude of uterine contractions regardless of experimental condition, suggesting that the cannabinoid system exerts an *inhibitory* influence on *bladder* motility but an *excitatory* influence on *uterus* motility. The slope of the dose-response function for bladder activity was greater in rats with inflamed bladders or HYPX than in rats with uninflamed bladders, suggesting that inflammation increases effectiveness of cannabinoids in the bladder and that the hypogastric nerve participates in regulation of cannabinoid receptor sensitivity. The slope for uterine function was reduced in rats with inflamed bladders or HYPX, suggesting a neurogenic influence on cannabinoid function in the uterus. SR prevented responses to WN2 in both bladder and uterus, suggesting that WN2 was acting on CB1 receptors. The effect of WN2 was greater when delivered by arterial injections close to the bladder and uterus than by injections into the tail vein, suggesting that WN2 acts at least in part on cannabinoid receptors within the bladder and uterus.

CLINICAL IMPLICATIONS: The results on bladder support recent experimental studies showing that endocannabinoids reverse and reduce inflammation-mediated bladder hyperactivity in rats (5,6) as well as anecdotal reports that cannabis alleviates bladder hyperactivity in patients with multiple sclerosis (3) and recent pilot clinical trials showing the same effect using sublingual sprays of extracts of cannabis containing both THC and CBD or THC alone (1). On the other hand, the results on the uterus, while consistent with experimental data showing that anandamide helps regulate receptivity of mouse uterus for embryo implantation (10), are difficult to reconcile with the fact that cannabis has been used for more than a century to treat dysmenorrhea and menorrhagia (8). This situation raises important clinical issues: (a) how the influence of cannabinoids on multiple organs might affect their use for alleviating morbidity associated mainly with one organ; (b) how the actions of synthetic ligands differ from the actions of products developed from *Cannabis sativa*; (c) how the actions of agents vary depending on which single agents or which combinations of single agents are used.

REFERENCES & ACKNOWLEDGEMENT: (1) *Brady et al., Soc Neurosci Abstr 2001;27.* (2) *Buckley et al., Neurosci 1998;82:1131-49.* (3) *Consroe et al., Eur Neurol 1997;38:44-8.*(4) *Das et al., PNAS 1995;92:4332-6.* (5) *Jaggar et al., Pain 1998;76:189-99.* (6) *Jaggar et al., Neurosci Lett 1998;253:123-6.* (7*) Martin et al., Br J Pharmacol 2000;129:1707-15.* (8) *O'Shaughnessy, Trans Med & Phys Soc 1842;8:421-69.* (9) *Pertwee & Fernando, Br J Pharmacol 1996;118:2053-8.* (10) *Schmid et al., PNAS 1997;94:4188-92.* Supported by NIH grant RO1 NS1189 and NIDA (gift of SR), and The Fishbein Family IC Research Foundation.

ACUTE AND CHRONIC EFFECTS OF CANNABIS BASED MEDICINAL EXTRACT ON REFRACTORY LOWER URINARY TRACT DYSFUNCTION IN PATIENTS WITH ADVANCED MULTIPLE SCLEROSIS- EARLY RESULTS

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The primary aim of this open label pilot study is to evaluate the safety, tolerability and efficacy of 2 sublingual preparations of cannabis based medicinal extract (CBME) in patients with advanced multiple sclerosis (MS; Kurtzke $\geq$ 6.5) and refractory lower urinary tract symptoms (LUTS) in whom indwelling catheterisation is being considered.

Inclusion criteria are troublesome LUTS and detrusor hyperreflexia demonstrated by cystometry. Patients with an indwelling catheter or mini-mental state examination score <27 are excluded. Data are collected using cystometry, frequency volume charts and pad testing. For the first 8 weeks of treatment patients receive CBME containing equal amounts of cannabidiol (CBD) and tetrahydrocannabinol (THC), whereas THC-only is prescribed for weeks 9-16. At the first treatment visit patients take up to 4 sprays of CBME as tolerated, under supervision (equivalent to 10mgs of THC and 10mgs of CBD).

17 patients have so far been recruited. We present the early results of 10 evaluable patients (2M:8F, 31-63yr), 8 of whom have now completed 16 weeks of CBME. Mean maximum cystometric capacity (MCC) was 278mls at baseline. After 8 weeks of treatment this increased to 344mls (without CBME use for the previous 24 hrs) and to 435mls following administration of the maximum tolerated dose of THC:CBD:1:1. This suggests both a chronic and acute effect. At the 16-week visit the MCC decreased from a mean of 405mls before, to 392mls after, the maximum tolerated dose of THC-only extract. Frequency volume chart data are presented below.

	Baseline (3 Weeks, 10 patients)	**CBD:THC:1:1** (Weeks 1-8, 10 patients)	**THC** (Weeks 9-16, 8 patients)
Mean daytime frequency	9.3	7.5	6.9
Mean episodes of nocturia	2.7	1.4	1.5
Mean # of incontinent episodes/ 24 Hrs	2.1	1.0	0.7

These early results indicate that CBME may have a role in the management of patients with advanced MS and refractory LUTS.

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CLINICAL INVESTIGATION OF Δ-9-TETRAHYDROCANNABINOL (THC) AS AN ALTERNATIVE THERAPY FOR OVERACTIVE BLADDERS IN SPINAL CORD INJURY (SCI) PATIENTS?

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We are presenting the preliminary results of a pilot study. THC was administered over a period of 6 weeks. In 15 patients with spastic spinal cord injury the effect of THC on the overactive bladder has been investigated. The effect of THC was compared with urodynamic and clinical parameters, first without any bladder medication and after 6 weeks medication with THC. There are no data of invasive investigation in literature up till now.

PATIENTS AND METHODS:
THC was administered for 6 weeks in two different groups orally as Dronabinol (Marinol®) in 9 patients and rectally as THC-Hemisuccinate suppositories (THC-HS-supp) in 6 patients in several individual dosages per day. An urodynamic investigation, urine analysis and urine bacteriology was performed at the beginning of the study (without any bladder medication and without any spasmolytic therapy) and in the end after 6 weeks treatment. On the last day of medication all patients have been administered either 10 mg Dronabilon or 10 mg THC-HS-supp 2 h before the urodynamic investigation (relating to the group they were in).
Investigated parameters: first desire to void (FDV), maximum cystometric capacity (MCC), intravesical pressure (IVP), bladder compliance (CPL), post void residual urine volume (RV), volume at first detrusor contraction (VFC).

RESULTS:
The Dronabilon group showed an increasment of the CPL from mean 34.3 ml/cm H_2O (9 – 100) to mean 52.2 ml/cm H_2O (11 – 200). All other parameters have not been changed essentially.
The THC-HS-supp group showed a trend with increase of MCC from mean 227 ml (143 – 323) to mean 278 ml (121 – 322) (p value = 0.075), and an increase of the VFC from mean 191.3 ml (121 – 322) to mean 224.6 ml (96 – 407), CPL increased from mean 21.3 ml/cm H_2O (6 – 60) to mean 40 ml/cm H_2O (10 – 120) significantly
(p value = 0.028). All other parameters have not been changed essentially.

CONCLUSION:
These preliminary results indicate a reduction of the overactivity of the detrusor of the bladder especially in the THC-HS-supp group with potential therapeutic consequences. The different results between oral and rectal application may demonstrate their different bioavailability.

CANNABINOIDS IN THE TREATMENT OF TOURETTE-SYNDROME

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INTRODUCTION – Gilles de la Tourette-Syndrome (Tourette-Syndrome, TS) is characterized by multiple waxing and waning motor and one or more vocal tics. Case reports suggested that marijuana smoking improves tics and associated behavioral disorders. These initial reports were supported by a retrospective survey using a standardized interview in a larger group of patients (n=64). Of 17 patients reporting prior use of marijuana 14 (82%) experienced a reduction or complete remission of motor and vocal tics. In an open uncontrolled pilot study we treated one patient once with 10 mg delta-9-tretahydrocannabinol (Δ^9-THC), the major psychoactive ingredient of cannabis sativa, which resulted in a tic reduction of about 80%. These initial results were confirmed by a randomized double-blind placebo-controlled crossover single-dose trial of Δ^9-THC in 12 adult TS patients demonstrating a significant improvement of motor and vocal tics after treatment with Δ^9-THC compared with placebo. This study was performed to investigate for the first time under controlled conditions over a longer-term treatment period whether Δ^9-THC reduces tics in TS.
METHODS - In this randomized, double-blind, placebo-controlled study 24 patients (19 men, 5 women, mean age = 33 $\pm$ 11 (SD) years, range, 18 – 68 years) were included. Patients were treated over a 6-week period. The dosage was titrated to the target dosage of 10.0 mg Δ^9-THC. Starting at 2.5 mg per day dose was increased by increments of 2.5 mg per day every 4 days. Tics were rated using examiner ratings (Global Clinical Impression Scale (GCIS), Shapiro Tourette-Syndrome Severity Scale (SPSS), Yale Global Tic Severity Scale (YGTSS)), a self rating (Tourette-Syndrome Symptom List (TSSL)) and a videotape-based rating scale at 6 visits (baseline visit 1, visit 2-4 = during treatment period, visit 5-6 = after withdrawal of medication).
RESULTS - Seven patients dropped out of the study or had to be excluded but only one due to side effects like anxiety and restlessness. Using the GCIS, SPSS, YGTSS, and video rating we found a significant difference ($p<0.05$) or a trend towards a significant difference ($p<0.10$) between THC and placebo group at visit 2, 3 and/or 4. Using the TSSL at 10 different treatment days (between day 16 and 41) we found a significant difference ($p<0.05$) between both groups. At further 13 days there was a trend towards a significant difference ($p<0.10$). ANOVA as well demonstrated a significant difference ($p=0.037$). No serious adverse reactions occurred. Blood pressure and pulse did not change significantly. Five patients in the THC group reported mild side effects like tiredness, dry mouth, dizziness, and muzziness. Three patients in the placebo group reported about adverse effects like tiredness, dizziness, anxiety, and depression.
CONCLUSIONS - Our results provide more evidence that Δ^9-THC is effective and safe in the treatment of tics in TS. Because there is substantial evidence that cannabinoids regulate motor activity in the basal ganglia, it can be hypothesized that the central cannabinoid receptor system might play a role in TS pathology.

Acknowledgement: This study was supported by a grant of the Medical School of Hannover. THC was kindly donated by UNIMED Pharmaceuticals, Inc.

MEDICINAL CANNABIS EXTRACTS IN CHRONIC PAIN

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We have had a long interest in cannabinoids for chronic pain having explored the use of Nabilone. Most patients informed us that they preferred plant cannabis. The availability of standardised plant extracts has allowed us to start formal clinical trials.

PATIENTS STUDIED

All the patients we have studied have chronic pain and associated symptoms (eg. lack of sleep). Most have been drawn from the local Pain Relief Clinics and most are well-known to the senior clinician. The first group were all current users enabling an informed opinion on effects and side-effects of the new materials and new route.

Materials Used

Whole plant extracts derived from cloned plants. These are either high THC strains (>95% THC – no CBD) of high CBD strains (>95% CBD + some THC). The remainder (> 5%) consists of other cannabinoids, terpenes etc. The material is formulated as a sublingual spray.

DESIGNING THE STUDIES

The main objectives of the studies are to identify therapeutic windows of the CBME being used (including safety and tolerability) and to determine the approaches to more extensive and detailed studies.

Chronic pain is a complex Biophysical, Psychological and Social problem and patients vary greatly even with the same underlying pathology. MS is a perfect example with the additional problem of being a variably progressive disease. Cannabis has variable sites of action, variable psycho-active effects and variable dose response/ adverse effect profile. Additionally there is the problem of requiring Home Office Licences and being under substantial professional, bureaucratic and public observation.

It was decided to first study patients individually using an “N of 1” format. Subsequent aggregation of elements of data will inform the design of future studies whilst developing a depth of clinical experience.

When a patient has shown clear benefit then they are entered onto a long-term study whereby the chronic use of cannabinoids can be observed.

CONDUCTING THE STUDY

Acute side-effects were encountered during acute dosing periods but these reflected our inexperience with the agents. Overall the materials have been well tolerated and have produced therapeutic benefits without disabling psychoactive effects.

Benefits and Problems

For the individual patient it has proved relatively easy to establish benefits. Side-effects have been common but usually well tolerated.

These themes will be developed in this presentation and overall results will be discussed, linking in with the poster presentations form this team.

THE ANALGESIC EFFECT OF ORAL THC ALONE OR IN COMBINATION WITH MORPHINE IN HEALTHY SUBJECTS UNDER EXPERIMENTAL PAIN CONDITIONS

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From folk medicine and andecdotal reports it is known that Cannabis may reduce pain. It has been shown in different animal studies that delta-9-tetrahydrocannabinol (THC) has antinociceptive effects or potentiates the antinociceptive effect of morphine. The aim of this study was to measure the analgesic potency of orally administered THC and THC in combination with morphine under controlled clinical conditions.

THC (20 mg), morphine (30 mg), the combination of the two (20 mg THC + 30 mg morphine) or placebo were given orally as single doses. Twelve healthy volunteers were included in the randomized, placebo controlled, double-blind, crossover study. The experimental pain tests (order randomized) were: single and repeated transcutaneous electrical stimulation, mechanical pressure, heat stimulation and ice water. Additionally, reaction time, side effects (visual analog scales) and vital functions (blood pressure, heart rate and blood oxygen saturation) were monitored. Each test session was started with training phase and baseline determination, followed by administration of the drugs and pain tests every hour up to 8 hours post drug. For the pharmacokinetic profiling, blood samples were collected at defined intervals up to 8 hours.

THC alone did not significantly reduce pain. In the ice water and heat test it even produced hyperalgesia which was completely neutralized by the combination with morphine. A slight additive analgesia could be observed after electrical stimulation when combining THC and morphine. No analgesic effect resulted in the pressure and heat pain test, neither with THC nor the combination. The following, usually mild, side-effects of THC were monitored: sleepiness, euphoria (reduced in combination with morphine), feelings of anxiety and aggression, confusion, changing of perception, hallucinations (reduced in combination with morphine), nausea, vomiting, dizziness, headache, difficulties in breathing, heart flutter, digestive problems and dry mouth.

In conclusion, this study shows that oral THC does not significantly reduce pain in healthy subjects under experimental conditions. Some analgesic effects were only observed in combination with morphine. Psychotropic and somatic side-effects were common, but not severe. If the analgesic potency of THC could be increased by using alternative application forms, e.g. pulmonal aerosols, resulting in reduced first-pass effect and better bioavailability, will show ongoing studies.

ALTERATION OF COGNITIVE FUNCTIONING OF THE FRONTAL CORTEX BY 9-TETRAHYDROCANNABINOL IN HUMANS

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INTRODUCTION: Cannabis/Cannabinoids alter the metabolism of the frontal cortex which expresses a high density of cannabinoid-receptors. The influences of cannabis/cannabinoids on cognitive functioning of the frontal cortex are little known.
HYPOTHESIS: Cognitive functioning of the frontal cortex is altered by increased neurotransmission by 9-Tetrahydrocannabinol (9-THC) in normal volunteers.
AIMS: Examination of cognitive functioning of the frontal cortex in 12 healthy normal volunteers by the neuropsychological tests Stroop test, Trail-making test, Leistungsprüfsystem subtest 3 and verbal fluency testing (letter and category testing) before and after single oral intake of 10 mg 9-THC (Marinol®).
METHODS: 8 women and 4 men in the age between 23 and 31 years were tested (mean age 26,75 ± 2,7 SD). The tests were performed on two succeeding days each time between 10.30 and 11.00 a.m., on the second day after oral intake of 10 mg 9-THC (Marinol®) at 8.00 a.m. All data were statistically analysed by Wilcoxon Matched-pairs signed-ranks testing.
RESULTS: Stroop Test: After 9-THC the number of all mistakes as well as the corrected mistakes were increased in the interference task (2.67 ± 1.87 SD vs. 1.06 ± 1.44 and 2.08 ± 1,73 vs. 0,75 ± 0.96, respectively, $p < .05$). The uncorrected mistakes in the interference task, the time for the interference task as well as the color bar naming time were unchanged. Trail-making test part A and B: Testing times were unchanged. Leistungsprüfsystem subtest 3: The number of correctly solved items was increased (34.8 ± 3.0 vs. 31.8 ± 3,8, $p <.05$). The numbers of incorrectly solved items and missing items were unchanged. Verbal fluency (letter): Increase in the number of named words from 30 s after the start of testing until the end of testing after 1 min for the 1st and 2nd letter of the letter pair (6.25 ± 2.05 vs. 3.41 ± 1.93 and 8.0 ± 1.41 vs. 5.0 ± 2.30, respectively, $p <.05$). Increase in the number of all words named during the complete testing time of 1 min for the second letter of the letter pair as well as increase in the number of all words named during the complete testing time of 2 min for both letters of the letter pair (18.50 ± 4.85 vs. 12.91 ± 4.60 and 35.75 ± 7.62 vs. 26.42 ± 8.95, respectively, $p < .05$). The number of named words during the first 30 s of testing for the 1st and 2nd letter of the letter pair as well as the number of named words during the complete testing time of 1 min for the 1st letter of the letter pair were not altered. Verbal fluency (category): No change in the number of named words in the two categories (animals and plants) tested during 2 min each.
CONCLUSIONS: The results of the Stroop test after single oral intake of 10 mg 9-THC (Marinol®) by normal volunteers show for the first time an increased number of corrected (not uncorrected) mistakes in the interference task and therefore increased distractibiliy whereas the cognitive speed and the corrective control were unaltered by 9-THC. The results of the verbal fluency testing (letter) show for the first time higher word production with increasing length of testing in normal volunteers after single oral intake of 10 mg 9-THC. On the backround of earlier imaging studies performed during verbal fluency testing the underlying mechanism could be increased functional disconnection between the frontal lobe and the superior temporal gyrus. However learning effects cannot be excluded. Therefore we are planing a control study to address this issue. The trail making test and verbal fluency testing (category) were unchanged by 9-THC. However possible worsening caused by 9-THC that has been described earlier in normal volunteers without regular cannabis use after single smoking of cannabis could have been compensated in this study by possible learning effects. We will address this issue in a future study. Learning effects have already been shown for the Trail making test earlier. We assume that the increase in the number of correctly solved items in the Leistungsprüfsystem subtest 3 is most likely due to learning effects. We are planing another study to address this issue.

INFORMATION GAINED FROM CURRENT MEDICINAL USERS OF CANNABIS FOR MULTIPLE SCLEROSIS

Clare Hodges

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The ACT has received a large correspondence over the last ten years, including letters from hundreds of medical cannabis users. In order to help his research in 1994 we sent questionnaires to these correspondents to the ACT for Dr. Pertwee of Aberdeen University. Over a hundred people responded to the questionnaires he had devised, and he published the results in European Neurology (Eur Neurol 1997:38:44-48). Almost all patients reported benefits, particularly in spasticity and pain (over 90%). The survey was based on single answers to specific questions. The following observations are more wide-ranging, based on the now much larger correspondence and on many conversations over the years with patients who use cannabis. People with a variety of medical conditions have contacted us, but these observations are based on Multiple Sclerosis.

Psychoactivity. Almost all current cannabis users say that it helps them because it not only eases their physical problems, but because it also lifts their spirits, and improves their quality of life. Most studies concentrate on the physical benefits of cannabis, and it may well be helpful to look at the beneficial psychoactive benefits especially in chronic illnesses.

Delivery Methods. Most patients smoke cannabis, as it is a very efficient way of controlling the dosage. People who do not wish to smoke have been very inventive, from taking it in food, skin patches and suppositories. It seems very important to patients that they have some sort of control over their medication and can self-titrate in the same way that patients can for pain relief. Different delivery methods other than oral should be researched.

Dosage. It is remarkable the very different amounts people use to find relief. For some, an ounce of herbal cannabis may last four months, for others only two weeks. Similarly the amount used can vary considerably in the same patient. Research should be more flexible in amounts tested on patients, acknowledging the variability of the disease.

In general, anecdotal accounts from current users of medicinal cannabis could usefully be investigated further to help direct research.

ANALYSIS OF THE CARDIOVASCULAR EFFECTS OF CANNABINOIDS IN RABBITS

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Depending on their application pattern, cannabinoids can elicit a range of cardiovascular effects in humans, including tachycardia and orthostatic hypotension. The mechanisms of these actions are not clarified. Our aim was to analyse the actions of cannabinoids on sympathetic and parasympathetic regulatory mechanisms in animals.

Several experimental models were used to identify the sites of action of cannabinoids. Pithed rabbits served for studying peripheral effects on sympathetic and vagal neurons. In some conscious rabbits, drugs were injected into the cisterna cerebellomedullaris (i.c.m.) in order to observe direct effects on cardiovascular regulatory centres. In other conscious rabbits, drugs were administered systemically, and the overall effects on cardiovascular regulation were recorded. We used throughout the synthetic mixed CB_1/CB_2 cannabinoid receptor agonists WIN55212-2 and CP55940 and the CB_1-selective antagonist SR141716A.

Peripheral cannabinoid effects. In pithed rabbits in which the entire sympathetic outflow or the cardioaccelerator sympathetic nerves were electrically stimulated, WIN55212-2 and CP55940 decreased the plasma noradrenaline concentration, the blood pressure and the heart rate *(Niederhoffer and Szabo, Br. J. Pharmacol. 1999;126:457-466)*. The decrease in the plasma noradrenaline concentration suggests that the primary action of the cannabinoids was inhibition of noradrenaline release from postganglionic sympathetic neurons. The bradycardia evoked by stimulation of preganglionic vagal nerves in the neck was also inhibited by the cannabinoid agonists *(Szabo et al., J. Pharmacol. Exp. Ther. 2001;297:819-826)*. WIN55212-2 and CP55940 lowered the plasma adrenaline concentration in pithed rabbits. This was a direct effect on the adrenal glands, since these agonists also inhibited the adrenaline release evoked by electrical stimulation of superfused isolated adrenal glands. Since CB_1-cannabinoid receptor messenger RNA was not detected in the adrenal gland, we attribute the cannabinoid-evoked inhibition of adrenaline secretion to inhibition of acetylcholine release from preganglionic sympathetic fibres innervating the chromaffine cells. All cannabinoid effects in pithed rabbits and in adrenal glands were abolished or attenuated by SR141716A, pointing to the involvement of CB_1 receptors, the typical neuronal cannabinoid receptors.

Central cannabinoid effects. When WIN55212-2 and CP55940 were administered i.c.m. in conscious rabbits, two effects were observed *(Niederhoffer and Szabo, J. Pharmacol. Exp. Ther. 2000;294:707-713)*. Bradycardia developed as a consequence of enhanced vagal tone. A second effect, sympathoexcitation, was indicated by the increased firing rate of postganglionic renal sympathetic nerves and the increase in the plasma concentration of noradrenaline. Overall, the action of cannabinoids on cardiovascular regulatory centres led to an increase in blood pressure. The central effects of cannabinoids were also mediated by CB_1 receptors.

When cannabinoids were administered i.v. in conscious rabbits, all the above described primary effects could occur simultaneously. Apparently, the contrasting effects (central sympathoexcitation vs. peripheral sympathoinhibition, central excitation of cardiac vagal neurons vs. peripheral inhibition of cardiac vagal neurons) balanced each other, because the overall effects on blood pressure and plasma noradrenaline concentration were only moderate.

In summary, cannabinoids influence cardiovascular regulation by acting centrally and peripherally on sympathetic and parasympathetic pathways. Cardiovascular actions must be considered as important side effects of recreationally or therapeutically used cannabinoids.

CARDIOVASCULAR EFFECTS OF CANNABINOIDS IN THE RAT

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The psychotropically active constituents of hashish/marijuana interact with an endogenous cannabinoidergic system the role of which is being revealed currently. The compound arachidonoylethanolamide (anandamide) was identified as an endocannabinoid. The cannabinoidergic system is not restricted to the CNS but also plays a role in peripheral tissues and recent work suggests that it is implicated in septic shock and in the vasodilatation occurring in advanced liver cirrhosis. The present study was aimed at the identification of potential sites of action for anandamide in the cardiovascular system of the rat.

In anaesthetized rats, anandamide elicits a triphasic blood pressure response, i.e. a short-lived decrease followed by an increase and finally by a prolonged decrease. The initial hypotensive effect of anandamide (as well as the accompanying bradycardia) was attenuated by vanilloid receptor antagonists, including capsazepine and ruthenium red, but was not affected by the cannabinoid CB_1 receptor antagonist SR 141716. These results show that this phase is related to the activation of the Bezold-Jarisch reflex via vanilloid receptors.

The second phase was neither affected by SR 141716 nor by the vanilloid receptor antagonists whereas the third one was antagonized by SR 141716 but not by the vanilloid receptor antagonists. In order to further clarify the potential location of the cannabinoid CB_1 receptors involved in the third phase, additional experiments were carried out in a preparation in which peripheral cardiovascular parameters can be studied without interference with reflex loops involving the CNS, i.e. in pithed rats. The electrically induced rise in diastolic blood pressure (which is predominantly due to the release of noradrenaline) was inhibited by the cannabinoid receptor agonist WIN 55,212-2 but not by its enantiomer WIN 55,212-3. The effect of WIN 55,212-2 was attenuated by SR 141716. WIN 55,212-2 failed to affect the increase in blood pressure in response to injection of noradrenaline, excluding a postsynaptic site of action of the drug and suggesting that it may act via cannabinoid CB_1 receptors located presynaptically on the sympathetic nerve fibres innervating the resistance vessels.

Our results show that the endocannabinoid anandamide elicits cardiovascular effects by activating the Bezold-Jarisch reflex via vanilloid receptors and by activating cannabinoid CB_1 receptors probably located presynaptically on the postganglionic sympathetic neurones innervating the resistance vessels of the rat. Results from our group and from other authors revealed additional cardiovascular sites of action for cannabinoids on the autonomic nerves innervating the heart, in the endothelium and in the CNS.

MEDICAL RESEARCH ON MARIJUANA IN THE NETHERLANDS: LEGAL CONSIDERATIONS

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The Dutch minister of Health, Welfare and Sport established the Office of Medicinal Cannabis from the 1st of January. The Office is aiming at the development of cannabis based medicines. The development itself has to be done by drug companies which will be supported by OMC.
OMC will connect growers, pharmaceutical companies, patients associations and clinicians. If the outcome of research is positive, the use of cannabis as a medicine will be allowed in a later stage.
The minister appointed OMC as a national agency according to the Single Convention on narcotic drugs. OMC will supply the companies with standardised and legally grown cannabis for clinical trials. OMC will be responsible for preventing leakage to illegal circuits.

PLANS FOR AN UNLICENSED CANNABIS PREPARATION IN GERMANY

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INTRODUCTION

Basically, there are two kinds of medicines that are prescribed by doctors in Germany, licensed drugs which are registered trade marks of pharmaceutical companies, and unlicensed drugs prepared by pharmacists.

DRONABINOL

Since 1998, dronabinol (THC) is available on prescription in Germany. It may be prescribed as Marinol™, a licensed dronabinol preparation and registered trademark of Unimed Pharmaceuticals, that is imported to Germany from the United States. Since 1999 the Frankfurt firm THC Pharm is allowed to manufacture dronabinol from fiber hemp through isomerization of cannabidiol extracted from the plant. This dronabinol is sold to pharmacists that make capsules and tinctures from it and sell the preparations as unlicensed drugs.

FORMULAS ON DRONABINOL AND CANNABIS EXTRACTS

In November 2001 formulas for the preparation of drugs from dronabinol will be published by the "Deutscher Arzneimittelkodex" (DAC) and the "Neues Rezepturformularium" (NRF), institutions of the German Pharmacists Association responsible for the development of formulas for medicinal plants. Formulas for dronabinol for both the manfacturing of capsules and oil tinctures will be published.

In 1999 the Federal Health Ministry asked DAC and NRF and the German Pharmacists Association, respectively, to develop standardized formulas for a natural cannabis extract. In 2001 DAC and NRF have got plant material from a German grower who until now possesses the only license for the cultivation of drug cannabis for medical use in Germany. Formulas on cannabis are expected to be developed and published until late 2002. It is intended that pharmaceutical companies prepare a standardized cannabis preparation that can be ordered by pharmacies to make capsules and tinctures from it.

CHANGE OF LAW

According to the Federal Health Ministry the Federal Expert Committee on Narcotic Drugs intends to discuss the question, whether to recommend rescheduling of cannabis so that physicians will be allowed to prescribe it, on their meeting in January or June 2002. The law makers in Germany usually follow the recommendations of this committee. Thus, rescheduling of cannabis might happen in late 2002 or in 2003.

CONCLUSION

The position that single cannabinoids, such as dronabinol, have a medical value, but cannabis has none (and vice versa), sounds strange for many Germans, including doctors and politicians. There is a broad consensus that herbal medicines have a place in modern medicine and the government agreed that a natural cannabis preparation should be made available on condition that "*the legal pharmaceutical regulations are observed"* (*Flenker and Möller, Deutsches Ärzteblatt. 2001;98:A-1104-1106.*).

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CHANGING CONCEPTS OF ANOREXIA – CACHEXIA IN CANCER PATIENTS. POTENTIAL IMPACT ON CLINICAL RESEARCH.

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Patients with advanced cancer experience that loss of weight (cachexia) and appetite (anorexia) as well as associated symptoms such as fatigue and chronic nausea affect the quality of life of them and their families. Especially in patients with far advanced disease former attempts to exclusively increase caloric intake resulted in no significant improvements in most clinical outcomes. It became obvious during the last years, that in the context of active cancer complex metabolic, neuro-endocrine and anabolic alterations occur, summarized as primary anorexia/cachexia syndrome (PACS). However, several other factors beside PACS can lead to cachexia and anorexia in advanced cancer patients, summed up as secondary anorexia/cachexia (SACS). Patients suffering from cancer frequently present with a mixed form of PACS and SACS.

At present time variable patient populations are represented under the term cancer anorexia/cachexia. Weight loss is defined variably, reaching from active weight loss during the last few months to weight loss compared to pre-illness weight. The presence of anorexia is required irregularly for diagnosis of the syndrome. The design of clinical studies in weight-loosing cancer patients may take a proper characterization of patients with a component of SACS into consideration, especially if the treatment aims to target primarily PACS. SACS may include (1a) impaired oral intake due to both altered integrity & function of the gastrointestinal tract as well as severe other symptoms (such as pain, dyspnea); (1b) loss of proteins with body fluids; (2) catabolic states unrelated to cancer (such as infections or chronic heart failure); (3) loss of muscle tissue as a consequence of decreased muscle activity in bed-ridden patients (deconditioning).

Research from animal models and in humans with several wasting conditions (HIV-wasting, chronic renal failure, cardiac cachexia, liver cirrhosis, etc.) suggests multiple mechanisms mediating PACS. The predominance of the different mechanisms (metabolic, neuro-endocrine and anabolic modifications, respectively) seems to differ between the various wasting conditions. Immune alterations including (pro-inflammatory) cytokines are predominantly involved in most wasting conditions as a cause for PACS. Tumor-derived cachectic glycoproteins, such as proteolysis-inducing factor, directly affect muscle proteolysis and correlate with weight loss. It is not known, if this tumor-derived factors may be present in non-cancer conditions. In patients with HIV-wasting alterations of anabolic hormones may be more prominent than in cancer patients.

At present time the majority of current clinical trials in weight loosing cancer patients has a pragmatic design. In order to perform more tailored clinical research and to establish new treatment concepts for the different wasting conditions, it may be of importance to more clearly define subgroups of patients. The targeting of interventions at multiple, different sites of action may allow the development of combined therapies.

NEUROBIOLOGY OF REWARD AND ADDICTION

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One common property of natural reinforcers and addictive drugs is that both activate the brain reward system. The central element of this system is the mesocorticolimbic dopaminergic system which projects from the ventral tegmental area (VTA) in the midbrain to telencephalic areas such as the nucleus accumbens (NAS) and the medial prefrontal cortex (mPFC). Associated with this core pathway are a number of other limbic and cortical structures that interact with the mesocorticolimbic system. While natural reinforcers elicit adaptive responses that eventually help the survival of the individual (e.g. learning about the location of good feeding places), drug reinforcers lead to maladaptive behavior such as compulsive drug intake and association of the drug effects with environmental cues (which, in turn, can trigger craving and relapse after withdrawal).

The neurotransmitter that has been most strongly implicated in the mechanisms of reward and addiction is dopamine (DA). Almost all addictive drugs increase dopaminergic transmission in the NAS, and many effects of addictive drugs can be antagonized by DA antagonists, such as haloperidol. Yet, although the increase in DA release may be a very important component in the generation of reward and addiction, it does not seem to be the only one. For example, on the cellular/electrophysiological level, THC and heroin produce comparable increases in the activity of dopaminergic cells despite their undisputed differences in addictive potential. Thus, there must be other factors that determine the degree of the addictive potential of a drug. More recently, the neurotransmitter glutamate has been implicated in the mechanisms of reward and addiction. In particular, glutamate has been found to have a role in the plastic changes in the CNS that take place during the development of an addiction. Many structures associated with the brain reward system use glutamate as their transmitter. For example, glutamatergic inputs from the mPFC, the hippocampus or the amygdala strongly influence the activity of dopaminergic cells in the VTA and the release of DA in the NAS. In accordance with this, glutamate receptor antagonists (in particular antagonists of the NMDA receptor subtype) have been found to attenuate at least some of the effects of drugs that might contribute to the development and maintenance of addiction in animal models.

On a more general level, addiction can be conceptualized as an increased response of an individual to the effects of drugs. This is manifest on the neurochemical level as well as on the behavioral level in a phenomenon called ´sensitization´. On the neurochemical level, repeated drug intake alters the response of the mesocorticolimbic system to the drug such that repeated administration of (constant) drug doses elicits stronger and stronger neurochemical responses, i.e. DA release in the NAS. On the behavioral level, the sensitization is manifest in the shift from initial ´drug liking´ to ´drug wanting´ to ´drug craving´.

In conclusion, addiction is a multi-faceted phenomenon, not only in its clinical manifestation but also in its neurobiological foundations. Basic research has made enormous progress within the last decade, and there is hope that an ever better understanding of the mechanisms involved in the development and maintenance of addiction can eventually lead to the treatment or prevention of addiction.

INTERACTION OF THE CANNABINOID AND OPIATE SYSTEM

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As early as in 1975, the observation of an interaction of morphines and cannabinoids in rats was reported in the scientific journal Science: A morphine withdrawal syndrom was successfully treated with delta–9-tetrahydrocannabinol (THC). On the other hand delta–9-THC dependent rats showed withdrawal signs after the treatment with the opiat-antagonist naloxone as reported two years later. A similar withdrawal syndrome was produced by the termination of the administration of THC.

After the endogenous cannabinoid anandamide was identified, cannabinoid research found new interest in the last years. The observation that cannabinoid-receptor-agonists reduce morphine-withdrawal symptoms was confirmed and cannabinoid-receptor-antagonists were shown to induce opiate withdrawal in morphine dependent rats. Mice that genetically do not express the CB1 receptor (CB-1 knockout mice), did not response to cannabinoids and the addictive effects of opiates were reduced. This close functional interaction of opiate and cannabinoid receptors is also represented by a co-localisation in different brain regions. In rats, CB-1 and μ-opiate receptor mRNAs were co-localized in brain areas as the nucleus accumbens, septum, hippocampus, dorsal striatum, the central amygdaloid nucleus and the habenular complex. Based on these animal studies, we have a close interaction of the effects of opiates and cannabinoids.

Most substances that can induce dependence produce a release of dopamine in the mesolimbic brain reward system (see presentation by Tzschentke). A cannabinoid receptor antagonist (as SR 141716A) prevented the cannabinoid-induced dopamin release as expected, but the opiate-receptor-antagonist naloxone also blocked the effects of cannabinoids on dopamin release. These results may show, that at least parts of the reinforcing effects of cannabinoids are mediated by opiate receptors.

Cannabinoids are not the only substance that interact with the opiate system. In alcohol dependence, the opiate-receptor-antagonist naltrexone reduces alcohol craving and prevents relaps. In a recent PET study, we observed a significant correlation between the availability of μ-opiate receptors and alcohol-craving/relapse in alcoholism. Since the effects of cannabinoids may be mediated by the endogenous opiate system, further brain imaging studies can address the effects of cannabinoid consumption on μ-opiate receptors in vivo.

CANNABIS SUBSTITUTION: HARM REDUCTION TREATMENT FOR ALCOHOLISM AND OTHER DRUG DEPENDENCE

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Since the introduction of cannabis to western medicine in 1839 byO'Shaugnessy cannabis has been known to have psychotherapeutic properties. Confirmed in American, British, and French medical literature, cannabis was specifically described as substitution for alcohol and opium addiction.

Addiction is herein defined as physical dependence with adverse physical andemotional effects from attempts to relieve emotional and physical disorder.

In 1843 Clendinning first described as a substitute for alcoholism, alcohol withdrawal, and opium dependence. More extensively studied in the first organized clinical medical study at the Ohio State Medical annual conference in 1860, confirmed and elaborated these observations. At the end of the 19th century cannabis substitution was recommended as a treatment for alcoholism and opiate addiction as well as antecedent or intercurrent causes of depression or trauma. The author reported on one case in 1970. Restoration of health and functioning from cannabis substitution was very effective.

Since cannabis prohibition there has been no accepted treatment until cannabis was legalized for medical purposes in 1996 in California. Cannabis centers in California provide both cannabis for substitution and fellowship.A significant number of patients medicate as substitution for more dangerous substances with good results. This effective biopsychosocial intervention has not, however, been accepted as a legitimate treatment of mainstream chemical dependency treatment programs at this time.

MEDICINAL CANNABIS EXTRACT IN CHRONIC PAIN: (1) DESIGN OF A COMPARATIVE "N OF 1" PRIMARY STUDY (CBME-1)

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Introduction

Plant Cannabis is widely used by patients suffering with chronic pain. Previous attempts to study its use have been complicated by the inability to standardise the cannabis extract and to measure the amount of cannabinoid used. We report the methodology of a study to investigate the use of Cannabis Based Medicinal Extracts (CBME) in patients with chronic pain. This study is the first to use a metered sublingual dose spray containing known quantities of pharmaceutically prepared Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) extracted from plants grown under controlled conditions. The aims of the study were to determine the relative therapeutic windows, and to evaluate benefits and safety.

Methods

An "N of 1" format was used for the study because of the heterogeneous nature of chronic pain conditions. The medicinal cannabis extract was administered as a sublingual spray. Initially the patients underwent a two-week open run-in period (Part 1) using a 1:1 mixture of cannabidiol and Δ9 tetrahydrocannabinol (THC/CBD). If they gained benefit from this they then progressed to Part 2 of the study, which included two blocks of four weeks. During this time each patient received one week of each of high THC, high CBD, placebo and 1:1 THC/CBD. The order of the CBME was randomised and double blind. Patients who were regular cannabis users were given rescue medication of the THC/CBD to prevent them returning to their previous cannabis use. Patients attended weekly for a variety of assessments (Pain and Activity scores, General Health Questionnaire (GHQ28), Becks Depression Inventory (BDI). Following these assessments, the medication for the subsequent week was then titrated to an appropriate level. VAS pain scores were recorded and samples for serum concentrations of THC and CBD were taken during the titrations. Non-invasive BP, pulse and ECG were monitored. Throughout 12 weeks, the patients kept a daily diary (VAS pain, sleep, side-effects, effectiveness, medication used). Those who gained benefit from the use of the cannabis extract were considered for entry into a long-term safety study.

Results

Patients with Multiple Sclerosis, chronic back pain & sciatica after spinal surgery and other neuropathic pains have been recruited. The first 6 patients (5 regular "medicinal" cannabis users, 1 previous "medicinal" cannabis exposure) gave early information on safety and effectiveness of the new materials. Of 19 patients so far studied 15 have shown a variety of benefits and have started a long-term safety extension study (see separate poster).

Discussion

Benefits and problems with the trial design will be discussed. More detailed results are reported in other posters and abstracts for this meeting.

MEDICINAL CANNABIS EXTRACTS IN CHRONIC PAIN: (2) COMPARISON OF TWO PATIENTS WITH BACK PAIN AND SCIATICA

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Introduction

In this abstract we describe the different experiences of two patients, with back pain and sciatica, recruited for our "N of 1" study of Cannabis Based Medicinal Extract (CBME). We compare the benefits and side effects.

Methods

2 female patients, A (53 yrs) and B (33 yrs) both suffering with chronic back pain and sciatica were recruited as part of a larger study of sublingual CBME in chronic pain (CBME-1 described in an earlier poster). Patient A, suffers from ongoing neurogenic leg pain following spinal fusion and is confined to a wheelchair. She was an occasional cannabis user prior to the study. Patient B, has pain as a result of a scarred nerve root following two lumbar discectomies. She had not used cannabis before. Details of the study design are described in an accompanying abstract from this team.

Results

From the start of treatment with CBME, patient A demonstrated a dramatic reduction in VAS pain scores from 6-7 to less than one. During the weeks of placebo she demonstrated some increases in pain scores but her pain did not return to pre-study levels. Her sleep remained variable. In contrast, patient B showed little change in VAS pain scores, but reported a substantial improvement in her sleep, which disappeared when using placebo. Patient A showed changes in her mood (BDI) and General Health Questionnaire (GHQ). Patient B did not score badly at the outset and little change was observed. Neither patient suffered significant side effects.

Discussion

These two patients with similar problems demonstrate the heterogeneity of both chronic pain and of the response to treatment with CBME. While patient A demonstrated substantial improvements in her pain scores, patient B gained improved quality of sleep. Both patients considered these improvements to be of substantial importance to them and opted to continue into a long-term safety study (CBME SAFEX).

MEDICINAL CANNABIS EXTRACTS IN CHRONIC PAIN: (3) COMPARISON OF TWO PATIENTS WITH MULTIPLE SCLEROSIS

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Introduction

In this abstract we describe the different experiences of two patients recruited for our study of Cannabis Based Medicinal Extract (CBME). We compare their benefits and side effects.

Methods

Two female patients, C (55 years) and D (44 years), both with Multiple Sclerosis, were recruited as part of a larger study of CBME for chronic pain. C had no previous cannabis use, but D had used it once. C identified neurogenic knee to ankle pain and lumbar pain as her two most prominent symptoms. D's symptoms included severe urethral and pelvic floor pain, partly as a result of a previous cystectomy, hysterctomy and colectomy. Details of the study design are described in an accompanying abstract from this team.

Results

Both patients showed a clear improvement in VAS pain scores at the start of treatment during the 2 week open run-in period on 1:1 THC/CBD. Later in the crossover period pain scores for each symptom for C were equally affected by the CBME. However, D's pelvic floor pain was worse on weeks when on high CBD, in contrast to her urethral pain which did not change. D had better overall symptom control when taking THC:CBD and worse symptom control with placebo, whereas C showed no clear pattern of changes in this measure. C had no change in quality or quantity of sleep throughout the study whilst D had improved quality and quantity of sleep while taking THC:CBD. C showed a sustained improvement in depression scores (BDI) throughout the study, whereas D had improved scores on THC:CBD and high CBD but worse scores on placebo. In contrast, although C showed a decrease in General Health Questionnaire (GHQ) score after the first two weeks of treatment, this was not sustained. D had a sustained improvement in GHQ, including a decrease from ten to zero in the severe depression element of the score. Both patients experienced some psychoactive side effects including dizziness, drowsiness and time distortion. In D this was particularly related to the use of THC by itself.

Discussion

These two patients demonstrate the problem of studying patients with multiple sclerosis. Although patient C initially gained benefit from treatment, D showed the more dramatic improvement and has continued into the long-term safety study. Towards the end of the 10 week study we realised that C was having a relapse of her MS. Although we gave her a subsequent challenge with THC:CBD we could not reproduce the initial 2 week period and concluded the study. Patient D had a flare up of her MS 3 months into the long-term study and it significant upset her pain control.

Multiple Sclerosis has been seen as the "most acceptable" disease in the UK for trials of cannabinoids. Unfortunately, there are probably few diseases that are harder to conduct clinical trials on.

MEDICINAL CANNABIS EXTRACTS IN CHRONIC PAIN (4) CANNABIDIOL MODIFICATION OF PSYCHO-ACTIVE EFFECTS OF Δ9-THC

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Introduction

It has long been suspected that Cannabidiol (CBD) might modify the psycho-active effects of Δ9 Tetrahydrocannabinol (THC). Anecdotal evidence from patients using cannabis medicinally suggests a preference for the milder forms of cannabis containing significant levels of CBD. Zuardi demonstrated that CBD reduces the intoxicant effects of cannabis in human volunteers. This effect has been observed in a patient participating in a study of sublingual Cannabis Based Medicinal Extract (CBME).

Case Report

A 40 year old woman with Multiple Sclerosis was participating in an "N of 1" study of CBME (GW Pharamceuticals). She had previously undergone a cystectomy, hysterectomy and colectomy. Her main pain problems were severe urethral pain and a "bearing down" type of pain deep within her pelvis. Both had been present for some 18 years. The CBME was administered sublingually. After an initial 2 week run in period with a mixture of 50% Cannabidiol (CBD) and Δ9 THC, she underwent a double blind, placebo controlled "N of 1" study. This consisted of 8x1 week periods where she received one of four preparations on two occasions for a week at a time. The four preparations were THC, CBD, 50-50 mixture of CBD and THC, placebo. (see previous abstract for details).

Over 12 weeks, she kept daily diaries of her pain, her pain control, sleep and side effects experienced. The total daily amount of drug was also measured. In her daily diary she recorded any episodes of a specified set of side effects (dry mouth, time distortion, panic, dizziness, drowsiness, hallucinations, high etc.). Their presence only each day was recorded. No attempt to measure the intensity of the effects was made.

Results

She achieved almost total pain control from the CBME. Psycho-active side effects were predominantly seen during the periods when she used THC alone. During the periods when she used a 1:1 mixture of THC and CBD, the incidence of side-effects fell dramatically, although she was using the same overall amount of THC.

Discussion

Some have suggested that large doses of CBD are necessary to achieve this effect. However, only small doses of cannabinoid were used in this study (less than the equivalent of a "joint" per day). This observation will be looked for with other patients taking part in this CBME study.

The preference for THC:CBD over THC is explored in a later paper from this team.

References

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MEDICINAL CANNABIS EXTRACTS IN CHRONIC PAIN: 5) COGNITIVE FUNCTION AND BLOOD CANNABINOID LEVELS

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Introduction

One of the major concerns with the use of cannabis as a medicine is the potential for side-effects. Disturbances of psychomotor and cognitive function may put the patient at risk. Our "N of 1" study of Cannabis Based Medical Extracts (CBME) involves titrating patients with different extracts under direct supervision over a 4 hour period (Details of the study design are described in an accompanying abstract from this team.)

Method

An initial cohort of 5 patients with chronic pain were given different extracts of CBME (GW Pharmaceuticals) at weekly intervals. During the initial dose of each extract regular blood levels of cannabinoids were measured at pre-dose, 30 mins, 1 hour (h), 2h and 4h. The patients completed a set of Cognitive functioning tests at Pre-dose, 1h, 2h, and 4h intervals. Two paper tests were used:

1. The Trail Making Test has two parts both require and measure "visu-spatial ability and motor sequencing skills", with part B incorporating a measure of "flexibility". Patients are timed as they attempt to join numbered circles in part A and a combination of numbers & letters in part B in a dot-to-dot fashion (Golden et al 1981).

2. The Information Processing Tasks A & B from the Adult Memory and Information Processing Battery (AMIPB). Both tasks required the patient to select and cancel out a target digit in a series of items. The patients were given a set amount of time to complete as many items as they could. A simple test of motor-speed accompanies each of the above tasks. The Information processing tasks were designed for clinicians to identify and evaluate impairments in mental ability (Coughlan & Hollows 1985).

Results

No apparent difference was seen in the ability of patients to complete the tests up to serum levels of 4.9 ng/ml THC but relief of symptoms was achieved in several patients. On two occasions patients experienced side-effects to a degree that prevented them undertaking the tests at the 4 hour stage. Subsequent serum THC levels were shown to have reached 6 ng/ml and 14 ng/ml.

Discussion

Generally, the CBME administered did not effect the patients' ability in performing these tests yet relief of symptoms were achieved. Therefore, these simple tests may serve as an indicator that patients are safe to carry out their normal activities at home when using their CBME to therapeutic levels.

MEDICINAL CANNABIS EXTRACT IN CHRONIC PAIN: (6) OVERALL RESULTS OF 23 "N OF 1" STUDIES (CBME-1)

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Introduction
The results of the first 23 patients who have undertaken the study are presented.

Methods
The methodology of the study has been described in Poster 1. All patients had had a range of Pain Management previously but were currently inadequately pain controlled.

Results
Patients with Multiple Sclerosis, chronic back pain & sciatica after spinal surgery, other neuropathic pains and a myopathy have been recruited.
The first 6 patients all had previous experience of cannabis and 5 were regular users. This gave us early information on effectiveness of the new materials via the sublingual route. . They were able to use the mixture of THC:CBD as escape medication to ensure that they did not return to using their previous cannabis.
Subsequently, no patients have had cannabinoid escape medication, but have used their normal analgesics
21/23 Patients completed the 12 week study. 2 of these showed some initial benefit but this was not demonstrated in any of the parameters measured in the double blind placebo controlled period. 2 patients did not complete the study (1 suffered unacceptable side-effects, and 1 could not cope with the study).

Benefits
The benefits were seen in many of the parameters studied and varied substantially between patients even within diagnostic groups. Improvements in pain, sleep, depression, activity and general health were the most important. 1 patient returned to skilled manual work and 1 continued a management level occupation.
All the 19 patients who showed benefit have started a long-term safety extension study (see separate poster 7).

Side effects
3 patients experienced postural hypotension (1 vasovagal collapse) during acute titration. This was associated with excessive dosage. Several patients noted mild dysphoria as they reached their individual ceiling dose.
During regular usage, dry mouth was the most frequent side effect. Drowsiness, time distortion, high, dizziness, mild panic were also seen and most commonly associated with THC use.

Discussion
The extracts and the route of administration are effective. It is possible to titrate the sublingual CBME accurately and customize this for the individual patient. The variety of pain problems seen validated the study method we used.
The 1-week periods were probably not long enough for some patients who could take several days to shown change in symptom intensity. This may reflect a prolonged pharmacological effect of the cannabinoid or a "resetting" of synaptic and neural activity.

MEDICINAL CANNABIS EXTRACT IN CHRONIC PAIN: (7) RESULTS FROM LONG TERM SAFETY EXTENSION STUDY (CBME-SAFEX)

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Currently the main target for the use of cannabinoids is in the management of chronic disease. Therefore the study of these drugs over months and even years is essential. The control of symptoms, the changes in drug use, activity & quality of life and the incidence of side effects are the critical issues. This study follows on from our primary CBME-1 study to assess the effectiveness of sublingual THC and CBD (see our Poster 1)

Methods

19 patients with chronic pain from Multiple Sclerosis, spinal pain (post spinal surgery) and a variety of other neurogenic pains had completed the CBME1 study (see Poster 1) and had shown benefit from the cannabis extract (either THC or THC:CBD mixture). These patients opted to continue using the medicine (CBME-SAFEX study). For the first 8 months the Medicines Control Agency would only allow the use of THC. Later CBD was allowed. Patients individualised their CBME usage under guidance from the team. The same monitoring tools that had been used in the initial study were continued, though simplified. Patients are counselled about driving and given specific instructions.

Results

19 patients have been studied for between 2 and 14 months (following the initial 10 week study)

Symptom control.

All have maintained symptom control although several took time settling onto the new regime. They had previously been having a variety of cannabinoids for periods of 1 week. In addition visits to the clinic were reduced in frequency and duration. Benefits such as improved bladder function have also been maintained.

Cannabinoid and other drug use

Most patients have maintained a static level of cannabinoid use. Some have managed to slowly reduce other medication but this has not been dramatic. Several patients have stopped their cannabinoid medication for periods of time up to 1 month. None have reported any withdrawal symptoms. However, most have experienced an increase in pain on doing so.

Quality of Life

Quality of life has improved for all. However, activity for many has not changed dramatically because of physical limitations.

Side Effects

The commonest side-effect has been dry mouth. For all patients the side effects have been very tolerable.

Other Problems

Many patients have encountered a range of physical and psychosocial problems (eg. exacerbation of MS (3), marital difficulties, birth of a baby, injuries, death of a wife, etc.)

Discussion

We have not seen any major problems with the Cannabis Medicine when used in the way described. However, larger numbers of patients studied over longer periods of time will be needed to increase confidence in the long-term safety of cannabinoid extracts.

MEDICINAL CANNABIS EXTRACT IN CHRONIC PAIN: (8) EVALUATION OF THC:CBD AGAINST THC IN THE MANAGEMENT OF CHRONIC PAIN

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INTRODUCTION

12 of 15 patients coming out of our primary CBME-1 trial preferred the 1:1 mixture of THC:CBD. However, we were initially unable to provide this mixture for about 8 months on the long-term safety study (See Posters 1 & 7 from this team). When we were able to provide this, 5 patients were changed from THC to the 1:1 mixture of THC:CBD.

METHOD

This paper examines a variety of parameters recorded in the 2 months before and 2 months after the change in medication. Comments written by the patients in their monthly diaries were also studied. The group consisted of 4 patients with chronic back and sciatic pain following spinal surgery, and 1 patient with multiple sclerosis. There were 4 females and 1 male. All of the patients had expressed a preference for THC:CBD in the initial CBME-1 study.

RESULTS

1) Medication use (number of sprays) rose slightly in one patient, fell in two, and remained constant in another two. (1 spray = 2.5mg THC or 2.5mg THC+ 2.5mg CBD)
2) Depression scores were stable over the whole of the 4 month study period in all of the patients.
3) Two patients showed a decrease in pain, one of which experienced little or no pain whilst on the THC:CBD. The other three patients had no dramatic improvement in pain scores. [link with #3]
4) The symptom control of the medication was constant in 4 patients. One patient demonstrated a substantial improvement in symptom control, which paralleled that observed during the CBME-1 trial.
5) The ability to perform specific activities increased dramatically in only 1 patient, paralleling the effect seen in the primary study (sexual activity) for this particular patient.
6) The dry mouth that 2 patients experienced on THC disappeared with THC:CBD. One patient had very few side-effects on either medication, and two found that the side-effects were similar before and after the change.
7) Sleep quality and duration improved markedly in one patient. It was unvarying in the other subjects, although one of these did comment on an improvement in sleep.
8) 4 out of 5 patients recorded comments on the benefit of the mixture, but the tests used in the study were probably too insensitive to identify these subtle effects.
9) All 5 patients remain on the THC:CBD mixture preferring it to the THC alone.

DISCUSSION

CBD seems to be important for many patients in improving the quality of their pain relief. However, the direct analgesic effect is not dramatic. It may be that CBD merely prevents some of the adverse effects of THC. Other combinations of the 2 cannabinoids will be interesting to study.

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