

International Association for Cannabis as Medicine

in cooperation with the
Institute for Psychiatry and Psychotherapy of the University of Cologne

IACM 4th Conference on Cannabinoids in Medicine

5-6 October 2007

Cologne

2007 Conference on Cannabinoids in Medicine

Place	Holiday Inn, Dürener Strasse 287, 50935 Cologne, Germany
Registration Fee	200 Euros for both days Students pay a reduced fee of 100 Euros for both days Members of the IACM pay a reduced fee of 150 Euros for both days The registration fees include a copy of the abstract book, daily rates (lunch for both days, coffee during the breaks) and an evening dinner on Friday.
Organizer	IACM Rueckertstrasse 4, 53819 Neunkirchen, Germany Phone: +49-2247-968083 Fax: +49-2247-9159223 E-mail: info@cannabis-med.org Internet: http://www.cannabis-med.org
Cooperation Partners	Institute for Psychiatry and Psychotherapy of the University of Cologne
Program Committee	Franjo Grotenhermen Markus Leweke Raphael Mechoulam Ricardo Navarrete-Varo Roger Pertwee Ethan Russo

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Friday, October 5

08:15 – 09:00 **Registration**

09:00 – 09:15 **Greetings**

09:15 – 10:30 **First Session (Human Studies)**

Chairs: Philip Robson, Rudolf Brenneisen

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|---------------|---|---|
| 09:15 – 09:30 | Philip Robson, David Blake, Meilien Ho, Ronald Jubb and Candy McCabe | Efficacy, safety and tolerability of long-term treatment with Sativex in rheumatoid arthritis |
| 09:30 – 09:45 | Marta Duran, Elena Ballarin, Eulalia Pérez, Ramon Puig, <u>Dolors Capellà</u> and SEGUIVEX study group | Follow up of patients with neuropathic pain, spasticity secondary to multiple sclerosis or wasting syndrome treated with a whole plant cannabis extract |
| 09:45 – 10:00 | Mark Ware, Tongtong Wang, Stan Shapiro, Thierry Ducruet, Ann Robinson, Ann Gamsa, Gary Bennett and Jean-Paul Collet | Smoked cannabis for chronic neuropathic pain: results of a pilot study |
| 10:00 – 10:15 | Dale Gieringer and Fred Gardner | Use of medicinal cannabis in California |
| 10:15 – 10:30 | Claude Vaney MD, Lis Schiesser and Rita Hausamman | Pattern of cannabis tea use among patients with multiple sclerosis |
| 10:30 – 11:00 | Break | |

11:00 – 12:15 **Second session (Preclinical Studies 1)**

Chairs: Bela Szabo, Emmanuel Onaivi

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|---------------|---|---|
| 11:00 – 11:15 | Barbara Costa, Francesca Comelli and Gabriella Giagnoni | Antihyperalgesic and antiinflammatory effects of a cannabis extract in animal models of inflammation and neuropathic pain |
| 11:15 – 11:30 | Daniela Parolaro, Paola Massi, Marta Valenti, Valeria Gasperi, Silvia Meli and Mauro Maccarrone | Lox pathway and endocannabinoid system are involved in the antitumor activity of cannabidiol |
| 11:30 – 11:45 | Meliha Karsak, Evelyn Gaffal, Rahul Date, Lihua Wang-Eckhardt, Jennifer Rehnelt, Stefania Petrosino, Katarzyna Starowicz, Regina Steuder, | Attenuation of allergic contact dermatitis through the endocannabinoid system |

Eberhard Schlicker, Benjamin Cravatt, Raphael Mechoulam, Reinhard Buettner, Sabine Werner, Vincenzo Di Marzo, Thomas Tuting and Andreas Zimmer

11:45 – 12:00 Raquel Abalo, Pablo Cabezas, Mónica Castillo, Ramón Fernández Pujol, Gema Vera and María Isabel Martín Cannabinoids prevent the development of both peripheral sensorial neuropathy and alterations in gastrointestinal transit induced by chronic chemotherapy in the rat

12:00 – 12:15 Ester Fríde, Hodaya Dahan, Shachar Steinberg, Hila Matan, Hilit Braun, Aron Weller, David Branski, Herbert H. Seltzman, Patricia H. Reggio and Raphael Mechoulam First animal model for 'failure-to-thrive' in infants: endocannabinoid-CB1 receptor deficiency and therapeutic directions

12:15 – 13:45 **Lunch**

13:45 – 14:15 Poster session

14:15 – 15:15 IACM General Meeting

15:15 – 16:00 **Review**

Raphael Mechoulam

Cannabidiol: Mode of action and therapeutic potential

Chair: Roger Pertwee

16:00 – 16:30 **Break**

16:30 – 18:00 Workshop: Promising Medical Uses of Cannabis-Based Medicines

Chair: Raphael Mechoulam

Daniela Parolaro: Cannabinoids as potential new therapy for the treatment of gliomas

Barbara Costa: Cannabis-based medicine in pain and inflammation. Is it better than pure cannabinoids?

Ethan B. Russo: Clinical endocannabinoid deficiency revisited: recent scientific developments support the concept

Roger G. Pertwee: Potential clinical applications for delta-9-tetrahydrocannabivarin

Philip Robson: Psychiatric targets for cannabis-based medicines (CBM)

18:15 Bus to Gaffel Brewhouse

Evening Dinner and IACM Award Ceremony

IACM Award Ceremony

During the evening dinner in the Gaffel Brewhouse we would like to honour four people for their major contributions to cannabinoid research and the re-introduction of cannabis-based drugs into modern medicine.

We would like to thank our gold sponsors Echo Pharmaceuticals and GW Pharmaceuticals for making this evening dinner and the IACM Award possible.

Evening Dinner

Dinner will be served in the Gaffel Brewhouse, Alter Markt 20 – 22, 50667 Cologne, Phone: 0221-2577692 at 19.00. The evening dinner and one drink is included in the registration fee.

Transportation to the Gaffel Brewhouse: Busses ('Bus Mingels') will leave from the Holiday Inn at 18.15. Arrival at the Gaffel Brewhouse between 18.30 and 18.45. Please come to the busses immediately after the end of the lectures.

Transportation to the Holiday Inn after the dinner: You may take a taxi or the tramway (line 7) from "Heumarkt" to "Dürener Strasse/Gürtel". Tickets can be bought in ticket machines in the tram. One way costs € 2.30 for one person or € 7.80 for four persons.

Saturday, October 6

08:45 – 09:15 **Registration**

09:15 – 10:30 First session (Preclinical Studies 2)

Chairs: Meliha Karsak, Daniela Parolaro

09:15 – 09:30	Roger G. Pertwee, Lesley A. Stevenson, Ruth A. Ross, Lisa A. Gauson and Adèle Thomas	Signs of cannabinoid CB2 receptor activation by tetrahydrocannabivarin, cannabigerol and cannabidiol
09:30 – 09:45	Lianne Robinson, Paola Fadda, Susan McKillop-Smith, Walter Fratta, Roger G. Pertwee and Gernot Riedel	Phytocannabinoid induced anorexic behaviour in fasted and non-fasted mice

09:45 – 10:00	Emmanuel Onaivi, Orlando Carpio, Hiroki Ishiguro, Norman Schanz, G. George Uhl and Robert Benno	Behavioral effects of CB2 cannabinoid receptor activation and its influence on food and alcohol consumption
10:00 – 10:15	Richard E. Musty, Jose Alexandre Crippa and Richard A Deyo	Effects of non-psychoactive cannabinoids on preclinical and clinical psychiatric/psychological disorders: a review and recommendations for further research
10:15 – 10:30	Ethan Russo	Beyond THC: the complementary therapeutic role of minor phytocannabinoids, terpenoids and flavonoids

10:30 – 11:00 **Break**

11:00 – 12:15 **Second session (Political Issues, Miscellaneous)**

Chairs: Rik Musty, Ethan Russo

11:00 – 11:15	Christian Giroud, Jonathan Paz Montoya, Bertrand Rochat, Marc Augsburger and Patrice Mangin	UGT 1A3 and 1A1 are the two main human recombinant UDP-glucuronosyltransferase isoforms responsible for the glucuronidation of (-)-11-nor-9-carboxy-delta-9-tetrahydrocannabinol in vitro
11:15 – 11:30	Patrik Roser, Jürgen Gallinat, Andreas M. Stadelmann, Thomas Nadulski and Georg Juckel	Acute effects of δ 9-tetrahydrocannabinol and standardized cannabis extract on the auditory evoked mismatch negativity
11:30 – 11:45	Arno Hazekamp, Krishna Bastola, Hassan Rashidi, Johan Bender and Rob Verpoorte	Cannabis tea revisited: a systematic evaluation of the cannabinoid composition of cannabis tea
11:45 – 12:00	Philippe Lucas	Regulating compassion; an overview of Canada's federal medicinal cannabis policy and practice
12:00 – 12:15	Marco van de Velde	Presence and future of legal medicinal cannabis in the Netherlands

12:15 – 13:45 **Lunch**

13:45 – 14:30 **Review**

Bela Szabo

Endocannabinoid-mediated retrograde signal transmission between neurons

Chair: Barbara Costa

Cannabis and Driving

Chairs: Günter Berghaus, Christian Giroud

14:30 – 14:45	Anja Knoche	Cannabis consumption and driver fitness
14:45 – 15:00	Franjo Grotenhermen, Gero Leson, Günter Berghaus, Olaf H. Drummer, Hans-Peter Krüger, Marie Longo, Herbert Moskowitz, Bud Perrine, Johannes G. Ramaekers, Alison Smiley and Rob Tunbridge	Developing limits for driving under the influence of cannabis

15:00 – 15:30 **Break**

15:30 – 16:15 Round-Table of Patients

Clare Hodges and others The experience of patients with the medical use of cannabis

16:15 – 17:00 Workshop: Cannabis Growing

Chairs: Arno Hazekamp, Tjalling Erkelens

16:15 – 16:30	Bernd Frank	Farming and processing of industrial hemp: An overview of 12 years of practical experience
16:30 – 16:45	Tjalling Erkelens	Basic guidelines for the cultivation of cannabis sativa for medicinal and pharmaceutical purposes.
16:45 – 17:00	Salvatore Casano and Gianpaolo Grassi	Optimization of agro-techniques of hemp (Cannabis sativa L.) for pharmaceutical applications

17:00 End of the Meeting

Posters

Poster Session on Friday, 13:45 – 14:15

Anju, Preet, Zaheeda Qamri, Ramesh Ganju, Jerome Groopman.	Cannabinoid receptor 2 (CB2) agonist, JWH inhibits growth and metastasis of non small cell lung cancer
William Notcutt, Cheryl Phillips, Sue Simmons, Mario Price, Cathy Sansom	Use of Sativex – prescribing issues
William Notcutt, Cheryl Phillips, Sue Simmons, Mario Price, Cathy Sansom	Compassionate use of Sativex – clinical experience
Zlatko Mehmedic, Desmond Slade, Heather Denham, Suman Chandra, Ikhlas Khan, and Mahmoud A. ElSohly	Indoor and outdoor cultivation of cannabis: is there an effect on the chemical composition of the volatile oil
Esperanza Herradón, Cristina González, Maria Isabel Martín and Visitación López-Miranda	Protective effect of cannabidiol in rat isolated hearts subjected to ischaemia-reperfusion
Christoph Konrad, Gudrun Werner and Michael Ueberall	Dronabinol in chronic pain - results of a retrospective, cross-sectional survey in patients with neuropathic pain
Jimena Fiz, Marta Duran, Klaus Langohr, Dolores Capellà, Magí Farré	Symptoms relief and improved mental health in fibromyalgia patients using cannabis. Results of an observational study
Anita Dudášová, Mike Parsons, and Areles Molleman	The effect of cannabidiol on mast cell function in isolated guinea-pig bronchi
Czesnik Dirk, Schild Detlev, Kuduz Josko and Manzini Ivan	Cannabinoid action in the olfactory epithelium
Rudolf Brenneisen, Pascale Meyer, Manuela Langos, Haithem Chtioui, Christian Steup, and Andrew Davies	Pharmacokinetics and adverse effects of pulmonal and intravenous THC-CBD formulations
Rudolf Brenneisen, Pascale Meyer, Christian Steup and Andreas Königstorfer	Source differentiation of thc by gc/ms profiling
Tatiana Bregman, Jenny Schneider, Albert Pinhasov, Oded Edelheit, Natalia Battista, Israel Hanukoglu, Mauro Maccarrone and Ester Fride	Cystic fibrosis: infertility and decreased motor activity may be prevented by THC treatment during development
Desmond Slade, Safwat A. Ahmed, Samir A. Ross, Mohamed M. Radwan, Fazila Zulfiqar and Mahmoud A. ElSohly	Cannabinoid ester constituents from high potency Cannabis sativa l.

Oral Presentations

EFFICACY, SAFETY AND TOLERABILITY OF LONG-TERM TREATMENT WITH SATIVEX IN RHEUMATOID ARTHRITIS

Philip Robson¹, David Blake², Meilien Ho³, Ronald Jubb⁴, Candy McCabe²

¹Cannabinoid Research Institute / GW Pharmaceuticals, Oxford Science Park, Oxford OX4 4GA; ²Royal National Hospital for Rheumatic Diseases, Bath BA1 1RL; ³Dept. of Rheumatology, Northampton General Hospital, Northampton NN1 5BD; ⁴Dept of Rheumatology, Selly Oak Hospital, Birmingham B29 6JD

Sativex[®], an oromucosal cannabinoid spray derived from a blend of whole-plant cannabis extracts, produced significant improvements in pain, quality of sleep, and DAS28 in a 5-week, randomised, placebo-controlled trial (Blake, Robson, Ho et al 2006) in patients with rheumatoid arthritis (RA). However, the safety and tolerability of Sativex in longer-term treatment of RA is unknown.

Methods: Following the acute study, patients from all but one of the participating centres were offered the opportunity to enroll in an open-label, long-term follow-up study. Each spray (100µl) of Sativex delivered 2.7mg delta-9-tetrahydrocannabinol (THC) and 2.5mg cannabidiol (CBD). Subjects self-titrated an evening-only dose (max 6 sprays) for two weeks, and thereafter were allowed 24h dosing and a further titrated increase to a maximum of 48 sprays/24h. Clinic visits took place at 4 weeks then at 12 weekly intervals for review of efficacy, safety, tolerability, and dose levels.

Results: Thirty-eight (72%) out of 53 eligible subjects entered the long-term study. Seventy percent of patients completed more than three months treatment, and 51% more than six. Average daily consumption of Sativex was 5.33 sprays. At the 24 week assessment (n = 26 (68%)) using 0-10 numerical rating scales, mean (SD) improvements from acute study baseline were as follows: Morning pain on Movement: 2.72 (2.7); Morning Pain at Rest: 2.24 (2.5); Quality of Sleep: 2.47 (2.2). Corresponding figures for the active medication in the 5-week acute study were 2.2, 2.2 and 2.3. Average daily dosing showed minimal fluctuation throughout the study.

Twenty-seven subjects (71%) experienced at least one treatment-related adverse event (AE), and 7 (18%) withdrew as a result (nausea and impaired balance; mild headaches; decreased appetite and weight; nocturnal hallucinations; oral mucosal blistering; diarrhoea and flatulence). Commonest AEs, most of which were mild (55%) or moderate (34%) in severity, were: dizziness 8 (21%); nausea 5 (13%); diarrhoea 4 (11%); arthralgia 2 (5%); dyspepsia 2 (5%); fall 2 (5%); headache 2 (5%); rheumatoid arthritis flare 2 (5%); vomiting 1 (3%). Three subjects between them experienced 5 severe AEs (nightmares, dizziness, dyspepsia, diarrhoea, flatulence). There were no serious AEs, or significant changes in haematology, serum biochemistry results, or vital signs.

Conclusions: Improvements in pain and sleep quality similar in magnitude to those noted in the acute study were recorded, and there was no evidence of tolerance to these beneficial effects or escalation of Sativex dosage over time. There were no safety concerns during this study, and Sativex was well tolerated by most patients over an extended period of treatment.

FOLLOW UP OF PATIENTS WITH NEUROPATHIC PAIN, SPASTICITY SECONDARY TO MULTIPLE SCLEROSIS OR WASTING SYNDROME TREATED WITH A WHOLE PLANT CANNABIS EXTRACT

Marta Duran^{1,4}, Elena Ballarin², Eulalia Pérez², Ramon Puig¹, Neus Rams³, Manel Rabanal³, Rafael Manzanera³, Dolors Capellà⁴ and SEGUIVEX study group⁵

¹Fundació Institut Català de Farmacologia, ²Clinical Pharmacology Service Hospital Vall d'Hebron, ³Direcció General de Recursos Sanitaris del Departament de Salut de la Generalitat de Catalunya, ⁴Universitat Autònoma de Barcelona, ⁵24 clinicians from 6 University Hospitals in Barcelona, 3 nurses, 6 Hospital Pharmacists and 71 community pharmacists. *Barcelona. Spain*

Introduction: Cannabis based medicines have been evaluated for the treatment of pain and spasticity associated with multiple sclerosis (MS), chemotherapy-induced nausea and vomiting, appetite stimulation and analgesia. Sativex is a cannabis extract (CE) approved in Canada as an adjuvant treatment for neuropathic pain in adults with multiple sclerosis. **Objective:** To describe the clinical and epidemiological characteristics of patients receiving a self-administered oromucosal spray of CE. Secondary objectives were assessment of perceived effects, toxicity, quality of life, doses used and patient and health care professional satisfaction. **Methods:** This is an observational follow up study of patients receiving CE as compassionate use, being conducted in six University hospitals in Barcelona. A network of neurologists, anaesthetists, oncologists, infectious disease specialists, hospital pharmacists and community pharmacists has been set-up. A specific training programme has been conducted for each group of health care professionals. Patients with these diagnoses not responding to standard treatments and giving consent are included by their hospital doctors. These are in charge of clinical and quality of life data collection. The CE is dispensed by hospital pharmacists. Community pharmacists train the patients on self-administration of the CE. Data collection regarding dosage and side effects is supervised by community pharmacists. **Results** From January to December 2006 129 patients have been enrolled [62 MS, 36 neuropathic pain and 31 with wasting syndrome (WS)]. Their main characteristics are shown in table 1. Median dose of CE was 7 puff per day (SD 5,8). Patients with MS and neuropathic pain improved the perceived effect of pain, quality of sleep, and quality of life at the last visit. MS patients also experienced an improvement in spasticity. WS patients experienced an improvement in appetite, quality of sleep, and quality of life. Sixty-eight patients (52.7%) withdrew. Reasons for withdrawal were: adverse effects (58.8%), lack of efficacy (29.4%), and others (11.7%). The most frequent adverse effects were dry mouth, somnolence and dizziness. **Conclusions:** These preliminary results show that patients treated with the CE were chronically and severely ill and treated with multiple drugs. A high percentage were cannabis users mainly for therapeutic reasons. In spite of the high percentage of withdrawals, some patients perceived beneficial effects with CE treatment. It would be useful to find tools to characterise responders to CE.

Table 1. Basal epidemiological and clinical characteristics.

	Pain MS n=19	Spasticity MS n=43	Neuropathic pain n=36	Wasting syndrome n=31	Total n=129
age X (min-max)	49,4 (30-67)	49,1 (33-64)	51,2 (25-75)	47,9 (39-79)	49,4 (25-79)
men/women	6/13	24/19	21/15	24/7	70/59
cannabis previous use	42,1%	23,3%	36,1%	74,2%	41,9%
smokers	26,3%	27,9%	38,9%	77,4%	42,6%
alcohol use	15,8%	30,2%	22,2%	25,8%	24,8%
concomitants treatments ^b					
<3 drugs	11	31	11	31	84
3-5drugs	7	12	22	0	41
>5 drugs	1	0	3	0	4
Intensity of symptoms	50% intolerable pain	47% continuous spasticity	71% intolerable pain	100% anorexia	
Quality of life (EQ-5D) [*]	29,1 (DE 17,2)	42,6 (DE 19,5)	37,7 (DE 19,6)	45,3 (DE 27,1)	

^{*}EQ-5D of general population is 71 (DE 17,4)

Acknowledgments: *Departament de Salut de la Generalitat de Catalunya and GW Pharmaceuticals.*

SMOKED CANNABIS FOR CHRONIC NEUROPATHIC PAIN: RESULTS OF A PILOT STUDY

Mark Ware, Tongtong Wang, Stan Shapiro, Thierry Ducruet, Ann Robinson, Ann Gamsa, Gary Bennett, Jean-Paul Collet

Departments of Anesthesia and Family Medicine, McGill University, Montreal, Quebec, Canada

Introduction

Chronic neuropathic pain affects an estimated 5-10% of adults and is refractory to many pharmacological treatments. Surveys suggest that 10-15% of patients attending pain clinics self-medicate with smoked cannabis to relieve pain, improve sleep, reduce stress and improve mood. Here we present the results of a pilot study to explore the safety and efficacy of smoked cannabis for chronic neuropathic pain.

Methods

We conducted a pilot randomized controlled crossover trial comparing four potencies of herbal cannabis (0%, 2.5%, 6% and 9.5% THC). Adult subjects with chronic neuropathic pain due to trauma or surgery with allodynia or hyperalgesia who were not current cannabis users were randomized to receive the four potencies in four five-day periods separated by nine-day washout periods. Subjects smoked a single inhalation of 25mg of cannabis using a pipe device three times daily for each five-day period. The first exposure of each period was done under direct supervision in a clinical laboratory; the remaining doses were taken at home. The primary outcome was the difference in the 5-day average pain intensity score, obtained by daily pain intensity measurements using an 11-point numerical rating scale administered by telephone during the exposure period between the 9.5% THC period and the 0% THC period. Effects on mood (POMS), sleep (LSEQ) and quality of life (EuroQOL-5D) were measured as well as adverse events.

Results

Twenty-three subjects were recruited, with a mean age of 45.4y (SD 12.3); 12 were female (52%). The median duration of pain was 2.9 years (range 1.1-41y). Two subjects dropped out in the first week, and 21 completed the trial. The average daily pain intensity was lower during the 9.5% THC period compared to the 0% THC period (5.4 (SD 1.7) vs. 6.1 (1.6); $p=0.02$). No significant differences in mood were observed. Subjects reported significantly improved ability to fall asleep (easier; $p=0.001$; faster, $p<0.001$; more drowsy, $p=0.003$) and improved quality of sleep (less wakefulness, $p=0.01$) on the 9.5%THC period than the 0% THC period. Overall quality of life was not different between the two groups. At the end of the study, 76% of subjects correctly guessed which was the 9.5%THC period and 62% correctly guessed the 0% THC period. No serious adverse events were observed. The most common (6 or fewer episodes) drug-related adverse events during the 9.5% THC period were headache, dry eyes, burning sensation, dizziness and numbness and cough.

Conclusion

This pilot study has shown that smoking 25mg (one puff) of 9.5% THC herbal cannabis three times daily for five days has a modest analgesic effect on chronic neuropathic pain and improves sleep. The drug was well-tolerated. Further long-term safety and efficacy studies are needed to evaluate the duration of these effects.

USE OF MEDICINAL CANNABIS IN CALIFORNIA

Dale Gieringer¹ and Fred Gardner²

^{1 2} Society of Cannabis Clinicians, Greenwood CA, USA 95635

Pursuant to the enactment of Proposition 215 in November, 1996, California has an extensive population of patients legally using cannabis as medicine. All such patients must obtain authorization from a licensed physician; however, there exists no statewide patient or physician registration system. Reluctance on the part of many physicians to authorize cannabis use has resulted in the emergence of de facto specialists whose practice is mainly devoted to cannabis medicine. In the absence of a statewide database, they comprise the best source of information on the current practice of cannabis medicine in the state.

Methods: Interviews were conducted in the fall of 2006 with 21 cannabis specialists, 14 of whom also completed an e-mailed survey. The survey posed 11 questions concerning medical conditions treated, patient demographics, dosage, efficacy, adverse reactions, cannabis substitution for alcohol and other drugs, and unusual indications.

Results: The surveyed physicians reported issuing cannabis approvals to some 160,000 patients, 95 -99% of whom had prior experience with cannabis. Most common indications were chronic pain (40%-85%), depression, anxiety and related mood disorders (15%-30%), gastrointestinal disorders (~15%), headache, including migraines (~10%), arthritis (~20%), insomnia (up to 20%-30%), neurological disorders/MS (~10%), nausea (10%-17%), alcoholism and other drug dependence (<10%) et al. ADD/ADHD, PTSD and bipolar disorder were frequently mentioned by physicians treating mood disorders. Cancer and HIV/AIDS patients were relatively few; presumably, most get recommendations from their primary care physicians. Numerous unusual medical problems were reported to be alleviated by cannabis. Physicians consistently reported that cannabis helped patients reduce or discontinue intake of other drugs, including opioids, sedatives, non-steroidal anti-inflammatories, muscle relaxants, hypnotics, etc.

Conclusions: Over the past decade, some 200,000 to 350,000 Californians have received physician approval to use cannabis in treating a wide range of conditions. In many cases efficacy can be confirmed by reduced use of other medications. No deaths or major adverse events have been attributed to cannabis (although the suicide of an adolescent who was also taking an SSRI antidepressant and an atypical antipsychotic must be noted). Many of the most common uses of cannabis reported by practitioners remain to be investigated in controlled clinical studies, among them: intractable chronic pain (e.g. from arthritis and injuries), migraines, gastrointestinal diseases, depression, anxiety, insomnia, PTSD, ADHD and bipolar disorder.

PATTERN OF CANNABIS TEA USE AMONG PATIENTS WITH MULTIPLE SCLEROSIS

Claude Vaney MD, Lis Schiesser and Rita Hausamman

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Montana

BACKGROUND:

Cannabis, in herbal form, seems to be widely used as self-medication by patients with multiple sclerosis suffering from symptoms such as pain, muscle spasticity, stress and insomnia. However, little is known about the exact pattern of its use among people with multiple sclerosis in Switzerland. We conducted therefore a telephone inquiry to estimate the frequency of cannabis use and to describe the main symptoms for which relief was being sought.

METHODS:

Among the 843 MS patient who joined our rehabilitation clinic in the last 5 years we made a telephone inquiry call, to all those who had told us at admission that they were taking hemp tea to treat MS symptoms.

RESULTS:

94 PwMS (11.1%) could be identified and reached by telephone. Mean sample age was 55 years and 64% were women. Sixty-one (64%) were still using a hemp tea on a regular basis and thirty-three (36%) had stopped taking the tea. Dizziness (10), inefficacy (8), psychoactive side effects (2) were the main reasons for giving up the medicine. An episode of tachycardia and the general practitioner being against it, figure among the anecdotic reasons for stopping the hemp consumption. Sixty three per cent of individuals who stopped cannabis said they would try the drug if it were available on prescription in tablet or spray form. Although the number of patients who were wheelchair-bound or only able to walk with an aid was high 74 (85%) among all patients interviewed, there was no difference in the degree of handicap between the patients who had abandoned the use and to ones who had not. Symptoms reported to be ameliorated included spasticity (36), chronic pain (5), both (13), bladder (2) and sleep problems (6). A Hemp Tea with milk (48), mostly as a tea before going to bed, was the preferred ingestion form followed by cookies (7), and smoking (6). Among the 48 patients taking hemp for spasticity, 12 were taking no other drugs and 10 could reduce the dosage of their other medications while taking the hemp tea.

CONCLUSIONS:

Symptom control using hemp tea seems to be quite popular among Swiss MS patients particularly among the more handicapped ones. This study confirms that spasticity and pain reduction are the most relevant therapeutical targets and that dizziness and not necessarily the psychoactive side effects represent limiting factors for the use of THC. The fact that many of the patients who stopped the use of THC would agree trying another galenical form, underlines the importance to commercialize this substance as a complement to the existing substances against pain and spasticity. In the mean time a hemp tea represents a cheap and save complementary drug to improve the quality of life of patients with MS when other treatments fail.

ANTIHYPERALGESIC AND ANTIINFLAMMATORY EFFECTS OF A CANNABIS EXTRACT IN ANIMAL MODELS OF INFLAMMATION AND NEUROPATHIC PAIN

Barbara Costa, Francesca Comelli, Gabriella Giagnoni

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The findings obtained in my laboratory strongly suggest that the use of Cannabis extract produced therapeutic advantages over effects seen with single components.

Particularly I reported here the results obtained comparing the effects of *in vivo* administration of pure THC, pure CBD and CBD-rich extract (H-CBD) in animal models of inflammation/neuroinflammation. I have previously shown the efficacy of CBD alone in inhibiting acute inflammation (Costa et al., *Naunyn Schmiedebergs Arch. Pharmacol.*, 369, 294, 2004), chronic inflammation induced by complete Freund's adjuvant and neuropathic pain (Costa et al., *Eur. J., Pharmacol.*, 556, 75, 2007).

Here I reported the antinociceptive and anti-inflammatory properties of H-CBD in a rat model of chronic constriction injury of sciatic nerve (CCI) and in a mouse model of acute inflammation induced by the intraplantar injection of carrageenan. Animals were orally treated in a therapeutic regimen. A group of animal was treated with H-CBD, a second and a third group with CBD or THC alone at the corresponding mixture dose. Data showed that THC chronic treatment did not reduce thermal hyperalgesia in CCI rats, while CBD treatment partially relieved it. The treatment with H-CBD extract evoked a total relief of thermal hyperalgesia, suggesting an improving of the effects of single cannabinoids. The major anti-inflammatory and antihyperalgesic potency of H-CBD versus pure compounds was also found in the murine model of acute inflammation.

In order to investigate whether this synergism could occur during pharmacodynamic phase, different antagonists were tested to study the involvement of cannabinoid and/or vanilloid receptors. Alterations in pharmacokinetic phase could be also responsible for H-CBD synergic effect observed. Hepatic cytochrome P450-mediated metabolism and intestinal P-glycoprotein-mediated transport, which cannabinoids are able to modulate and whose are substrates, were also studied. Data showed a marked decrease of total hepatic cytochrome P450 and an inhibition of P-glycoprotein activity only following H-CBD administration. Natural extracts contain substances such as terpenes and flavonoids that might increase cannabinoid bioavailability, probably by cytochrome P450-mediated metabolism inhibition. Moreover, both terpenes and flavonoids possess antioxidant and anti-inflammatory properties which could significantly contribute to the therapeutic effects. In conclusion the results reported here support the idea that the main Cannabis constituents, CBD and THC, and perhaps other plant components (including other cannabinoids but also terpenes or tocopherol) achieve synergy consisting of potentiation of pharmacological efficacy and decrease of adverse effects suggesting that the therapeutic usage of whole Cannabis extracts might offer various advantages over the employment of pure cannabinoids.

Acknowledgments: we are grateful to GW Pharmaceuticals for kindly supplying Cannabis extract

LOX PATHWAY AND ENDOCANNABINOID SYSTEM ARE INVOLVED IN THE ANTITUMOR ACTIVITY OF CANNABIDIOL

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We recently reported that the non-psychoactive cannabinoid compound cannabidiol (CBD) is able to kill glioma cells, either *in vivo* or *in vitro*, independently of cannabinoid receptor stimulation. However, the biochemical mechanisms underlying the antitumoral effect of CBD has not been clearly clarified. On this background, in the present work we performed biochemical analysis both on glioma tumor tissues excised by nude mice exposed *in vivo* to CBD and on U87 glioma cell culture treated *in vitro* with the cannabinoid, evaluating the involvement of both COX and LOX pathways, or of the endocannabinoid system. The *in vivo* exposure to CBD significantly decreased in tumor tissues the 5-LOX activity and content by about 40%, paralleled by the decrease (25%) of its product LTB₄. In contrast, the COX activity and level and PGE₂ amount were unaffected by the treatment. Besides, the *in vivo* treatment with CBD, markedly stimulated (175%) in tumor tissues the hydrolytic activity of fatty acid amide hydrolase (FAAH, the main anandamide-degrading enzyme). Concomitantly, a decrease in anandamide (AEA) level (30%) and in CB₁ receptor binding (25%) was observed. The involvement of LOX enzyme in the antiproliferative effect of CBD was confirmed by data obtained in *in vitro* experiments. The pretreatment of U87 glioma cells with MK-886, a specific inhibitor of 5-LOX activity at doses *per se* not affecting cell viability, was able to significantly enhance the antimitotic effect induced by CBD (MTT test). In contrast, when the pretreatment was carried out with indomethacin (COX-1/-2 inhibitor) or celecoxib (COX-2 inhibitor), no change was observed on CBD effect. The *in vitro* study of the endocannabinoid system revealed that CBD was able to induce a concentration-related increase of FAAH activity in U87 cells. Moreover, when FAAH overexpressing U87 cells were used, it was found a significant reduced rate of growth compared to U87 WT (by MTT and Trypan blue exclusion tests). In conclusion, the present investigation indicates that CBD exerts its antitumoral effects through the modulation of LOX pathway and endocannabinoid system, suggesting a possible interaction of both systems in controlling tumoral growth.

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ATTENUATION OF ALLERGIC CONTACT DERMATITIS THROUGH THE ENDOCANNABINOID SYSTEM

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Allergic contact dermatitis affects about 5% of men and 11% of women in industrialized countries and is one of the leading causes for occupational diseases. In this study we identified the endogenous cannabinoid system as a major regulator of cutaneous contact hypersensitivity (CHS) in a mouse model.

We used 8-10 week old CB1-receptor-deficient, CB2-receptor-deficient, and deficient mice and their wildtype controls. For the induction of CHS, mice were sensitized by painting 50 μ l of 0.2% DNFB (1-fluoro-2,4 dinitrobenzene) on the shaved abdomen on two consecutive days. For elicitation of CHS, ears of mice were painted with 10 μ l of 0.3% DNFB on day 5. Ear thickness was measured 24 h, 48 h, and 72 h after challenge using an engineers micrometer. Drug treatments were performed 30 min before challenge, as well as 24 h and 48 h after challenge. Tissue endocannabinoid levels were quantified using internal deuterated standards in LC-MS. DNFB treated and control ears from CB1/CB2-receptor-knockout and wildtype control mice were used for gene expression analysis. Total RNA was used for realtime RT-PCR and microarray experiments (MG_430 2.0 Affymetrix GeneChips).

In an animal model for cutaneous contact hypersensitivity we show that mice lacking both known cannabinoid receptors display exacerbated inflammatory skin responses to nickel-containing ear tags and in an experimental model of cutaneous contact hypersensitivity. Furthermore, contact allergic responses were accompanied by locally elevated endocannabinoid levels and were increased by the cannabinoid receptor-specific antagonists SR141716 and SR144528. Because our data indicate that activation of the endocannabinoid system may function to dampen the CHS response, we considered the possibility that administration of cannabinoids such as Δ^9 -tetrahydrocannabinol (THC) might attenuate CHS in wild type animals. Indeed, THC significantly decreased ear swelling in comparison to untreated mice. In order to gain insight into the molecular mechanism that may contribute to the increased CHS in cannabinoid receptor deficient mice, we performed a series of microarray experiments with RNA isolated from DNFB-treated ears of double knockout and wildtype mice, as well as the untreated control ears. Most interestingly, one chemokine was found to be differentially upregulated in DNFB-treated knockout ears.

Activation of the endocannabinoid system in the skin upon exposure to a contact allergen down-regulates allergic responses through modulation of chemokine production. Our results demonstrate a protective role of the endocannabinoid system in contact allergy in the skin, and suggest a novel target for therapeutic intervention.

CANNABINOIDS PREVENT THE DEVELOPMENT OF BOTH PERIPHERAL SENSORIAL NEUROPATHY AND ALTERATIONS IN GASTROINTESTINAL TRANSIT INDUCED BY CHRONIC CHEMOTHERAPY IN THE RAT.

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Introduction. Clinical use of antineoplastic drugs is associated with the development of numerous adverse effects that many patients find intolerable, including nausea and/or emesis, anorexia, and peripheral neuropathy. Recently, we have found that chronic treatment with cisplatin, one of the most emetogenic antineoplastic drugs, induce a long-lasting estate of gastrointestinal malaise in rats, detectable at least one week after the last administration of the drug (Vera et al, *Auton. Neurosci.* 126-127: 81-92, 2006), together with peripheral neuropathy signs. In view of the known neuroprotective effects of cannabinoids, we hypothesised that these drugs could prevent the development of both gastrointestinal malaise and peripheral neuropathy induced by chronic cisplatin.

Methods. For 4 consecutive weeks, male Wistar rats (250-300 g) received two intraperitoneal injections (30' apart) each week: 1- saline or cannabinoid vehicle or the mixed cannabinoid agonist WIN 55,212-2 (WIN, 0.5-2 mg/kg); 2- saline or cisplatin (1-3 mg/kg). Every week, body weight was recorded. Both before the first administration and one week after the last administration, behavioural tests were applied in order to detect the development of peripheral neuropathy (mechanical allodynia – von Frey filaments) and psychoactive effects typically associated with cannabinoid administration (cannabinoid tetrad). Finally, gastrointestinal transit was analysed by radiologic methods: rats received a suspension of BaSO₄ (2.5 ml, 2 g/ml) intraorally, and X-rays were obtained 0, 1, 2, 4, 6 and 8 hours after barium administration.

Results. Cisplatin induced a delay in weight gain and mechanical allodynia at the three doses used, a delay in intestinal transit (without affecting gastric emptying) at 2 and 3 mg/kg and altered values in the four tests of the cannabinoid tetrad at 3 mg/kg. When WIN (0.5-2 mg/kg) was administered together with cisplatin 2 mg/kg, both mechanical allodynia and delay in intestinal transit were prevented. The cannabinoid, at the doses tested did not induce any consistent alteration in the cannabinoid tetrad, gastrointestinal motility or the threshold for mechanical allodynia.

Conclusions. The induction of long-lasting mechanical allodynia and delay in intestinal transit indicate that different populations of peripheral neurones (probably dorsal root ganglion neurones and/or myenteric neurones) could be affected by chronic cisplatin. Very interestingly, cannabinoids prevented the development of both-neurotoxic effects (even when consistent psychoactive alterations were absent) further confirming the interest of cannabinoids as neuroprotective agents.

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FIRST ANIMAL MODEL FOR 'FAILURE-TO-THRIVE' IN INFANTS: ENDOCANNABINOID-CB1 RECEPTOR DEFICIENCY AND THERAPEUTIC DIRECTIONS

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We have shown in previous studies that a single exposure to the cannabinoid CB1 receptor antagonist/inverse agonist rimonabant (SR141716) immediately after birth, resulted in impaired milk suckling and severe growth failure in mice. We further showed that the growth failure, which is due to an inability to ingest maternal milk, results from an oral-motor impairment. The similarities between the rimonabant-treated mice and the symptoms which characterize infants who suffer from 'failure-to-thrive', motivated us to further investigate (I) the cannabinoid CB1 receptor as a target for failure-to-thrive or growth failure in newborn mice and (II) cannabinoid-based treatment of failure-to-thrive or undernourishment.

General Methods: Neonatal mice were injected with rimonabant (10-20mg/kg) at several time intervals after birth. Parameters including body weight, milk ingestion ('milkbands'), body (axillary) temperature and survival were assessed throughout the first 10 days of life.

Three studies were performed: (1) To generalize the growth stunting effects of the inverse agonist/antagonist rimonabant, we now injected the neutral CB1 receptor antagonist 5-(4-chlorophenyl)-3-[(E)-2-cyclohexylethenyl]-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole (VCHSR1) to neonatal mice. (2) We allowed rimonabant- and vehicle-treated pups to lick a milk/cream mixture from a dish ('lapping'), on the first 3 postnatal days. Successful ingestion of the mixture by the experimental pups would indicate that rimonabant selectively impairs oral-motor strength required to suck milk from the nipple, rather than the motivation and ability to ingest and assimilate food. (3) We raised mice in very small vs very large litters and thus established an undernourished ('failure-to-thrive') state without the use of rimonabant. Pups were treated daily with Δ^9 -tetrahydrocannabinol (THC, 1-5 mg/kg) or the endocannabinoid 2-archidonoyl glycerol (2AG, 0.1, 1 or 5 mg/kg) for the first 5 days of life.

Results: 1) Similar to rimonabant, VCHSR1 significantly interfered, in a dose-related manner, with milk ingestion, weight gain, body temperature regulation and survival. 2) The rimonabant-treated pups were able to independently ingest the mixture to the same extent as their vehicle-treated littermates and the licking procedure significantly improved their condition. 3) Finally, whereas THC or 0.1 or 5 mg/kg of 2AG did not improve weight gain consistently, 1 mg/kg of 2AG significantly enhanced weight gain in the undernourished pups raised in large litters.

Conclusions: (I) We now have evidence that endocannabinoid and/or CB1 receptor insufficiency underlies infant failure-to-thrive in mouse models (II) Cannabinoid-based treatment should be considered to improve food intake and weight gain in infants with failure-to-thrive or with growth failure.

PLANT CANNABINOIDS WITH NO THC-LIKE ACTIVITY

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Over the last 40 years most cannabinoid research has focused on the psychoactive cannabinoids. However during the 5-6 years considerable amount of pharmacological work on cannabidiol (CBD) has been published. CBD does not parallel THC in its psychoactivity. We are aware – in part at least – of the mechanisms of action of CBD and many of its valuable pharmacological actions can be rationalized.

Most of the other plant cannabinoids have been neglected as they also do not cause THC-like activity. But do they have valuable therapeutic properties? This remains to be clarified.

I shall first discuss the mechanisms and pharmacological actions of CBD, with emphasis on inflammation, diabetes, sleep and neuroprotection.

The second part of my lecture will be devoted to the activity of endocannabinoid-like natural and synthetic compounds, which do not bind to the known cannabinoid receptors, but which show potent therapeutic activity in cancer and ischemia.

CLINICAL ENDOCANNABINOID DEFICIENCY REVISITED: RECENT SCIENTIFIC DEVELOPMENTS SUPPORT THE CONCEPT

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Several years ago, a concept of clinical endocannabinoid deficiency (CED) was developed, hypothesizing that it might explain the pathophysiology of migraine, fibromyalgia, irritable bowel syndrome, and some other disorders in which cannabinoid medicines seem to provide unique relief. Certain biochemical evidence and pathophysiological relationships lend credence to the concept. For example, in migraine, the endocannabinoid, anandamide potentiates 5-HT_{1A} and inhibits 5-HT_{2A} receptors. Anandamide is also tonically active in the periaqueductal gray matter, a migraine generator and key central pain locus. Additionally, fibromyalgia is now conceived as a central sensitization state with secondary hyperalgesia. Idiopathic bowel syndrome has similar features. The three conditions are frequently co-morbid, and a susceptible patient may progress from one syndrome to others over the course of their lives. Based on this evidence, it was suggested that an underlying clinical endocannabinoid deficiency might be treated successfully and appropriately with cannabinoid medicines. This talk will briefly review these data, but also highlight recent research that supports the concept:

- 1) Further investigation has demonstrated that anandamide is integral to pathophysiological mechanisms of vascular control, sterile inflammation and central neuropathic pain generation in brainstem structures in the trigeminovascular system (Akerman et al.)
- 2) In female migraineurs, observed increased anandamide degradation in platelets, and reduced serum anandamide levels may explain decreased pain thresholds (Cupini et al.)
- 3) Cerebrospinal fluid samples from migraineurs demonstrate suppression of anandamide levels (Sarchielli et al.)
- 4) THC statistically significantly reduced electrically-induced and spontaneous daily pain scores in fibromyalgia patients (Schley et al.)
- 5) Sativex reduces peripheral neuropathic pain and allodynia scores (Numikko et al.)
- 6) Anandamide co-localizes with cholinergic in human colon and inhibit contraction of circular and longitudinal muscle via a non-CB₁ mechanism (Smid et al.)

Further approaches to investigating clinical endocannabinoid deficiency including biochemical experiments and clinical trial designs will be briefly presented.

CANNABINOIDS AS POTENTIAL NEW THERAPY FOR THE TREATMENT OF GLIOMAS

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Gliomas constitute the most frequent and malignant primary brain tumours. Current standard therapeutic strategies (surgery, radiotherapy and chemotherapeutics such as temozolomide, carmustin or carboplatin) for their treatment are only palliative and survival diagnosis is normally 6-12 months. The development of new therapeutic strategies for the management of gliomas is therefore essential. Interestingly, cannabinoids have been shown to exert antiproliferative effects on a wide spectrum of cells in culture. Of interest, cannabinoids have displayed a great potency in reducing glioma tumour growth either in vitro or in animal experimental models curbing the growth of xenografts generated by subcutaneous or intratecal injection of glioma cells in immune-deficient mice. Moreover, cannabinoids appear to be selective antitumoural agents as they kill glioma cells without affecting the viability of non-transformed counterparts. Results obtained with cannabinoids in a pilot clinical trial on patients with glioblastoma multiforme, their fair safety profile together with their remarkable anti-tumour effects, may set the basis for further studies aimed at evaluating better the potential anticancer activity of cannabinoids.

PSYCHIATRIC TARGETS FOR CANNABIS-BASED MEDICINES (CBM)

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The expanding prevalence of mental health disorders poses an enormous global challenge. Almost one in two people in the developed world will receive a psychiatric diagnosis during their lifetime, and five of the ten leading causes of chronic disability world-wide are psychiatric disorders (major depression, schizophrenia, bipolar disorder, alcohol abuse, obsessive/compulsive neurosis). There is considerable unmet clinical need as a result of the limited efficacy and potential toxicity of standard medicines.

Several lines of research indicate that anxiety and depression are promising targets for CBM. Emerging evidence suggests that cannabidiol may have potential as an anti-psychotic. CB₁ antagonists may have a role in relapse-prevention in the treatment of addiction. Other possible targets for the future include bipolar affective disorder, post-traumatic stress disorder, eating disorders, and insomnia. Manipulation of the endocannabinoid system through inhibition of FAAH or the anandamide transporter offers exciting therapeutic possibilities for some of these conditions.

Exploratory research targeting psychiatric conditions poses unique methodological difficulties. The use of endophenotypes as outcome measures in laboratory studies is to be encouraged.

CANNABIS-BASED MEDICINE IN PAIN AND INFLAMMATION. IS IT BETTER THAN PURE CANNABINOIDS?

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Cannabis is one of the first plant to have been used as medicine and the notion that it has potentially valuable therapeutic properties is a matter of current debate. Of particular interest have been the analgesic and antiinflammatory potential properties: clinical trials, anecdotal reports and researches employing animal models, strongly support the idea that Cannabis and cannabinoids exhibit a wide variety of therapeutic applications, including the relief of pain and the decrease of inflammation. However, the psychotropic effects observed in laboratory animals and the adverse reactions reported during human trials, as well as the risk of tolerance development and the potential dependence, limit the application of many cannabinoids in therapy. Nowadays, researchers focused the attention on other therapeutic strategies by which endocannabinoid system might be modulated to clinical advantage (inhibitor or activator of endocannabinoid biosynthesis, cellular uptake, or metabolism). However, emerging evidence highlighted the beneficial effects of whole cannabis extract over those observed with single components, indicating the cannabis-based medicine as new perspective to revisit the pharmacology of cannabis plant.

This talk aims to compare Cannabis and pure cannabinoids in pain and inflammation in terms of efficacy, toxicity and safety. The question is whether there is a rationale in developing Cannabis based medicine instead of pure compounds.

POTENTIAL CLINICAL APPLICATIONS FOR DELTA-9-TETRAHYDROCANNABIVARIN

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In addition to the established medicinal uses of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), there is an ever growing list of potential therapeutic applications not only for THC and CBD but also for other plant cannabinoids. One such plant cannabinoid is delta-9-tetrahydrocannabivarin (THCV), results obtained recently from pharmacological experiments having identified an important potential therapeutic application for this heretofore little-investigated compound. More specifically, it has been discovered that THCV can behave as a CB₁ receptor antagonist both *in vivo* and *in vitro* (reviewed in Pertwee, 2007), raising the possibility that THCV might (i) share the ability of other CB₁ receptor antagonists to suppress feeding and body weight in animals and man (reviewed in Matias and Di Marzo, 2007) and so (ii) perhaps eventually join the CB₁ receptor antagonist, rimonabant (SR141716A; Acomplia), in the clinic as an anti-obesity agent. Some experiments directed at establishing whether THCV can reduce feeding and body weight have already been carried out. These have shown that THCV does indeed share the ability of established CB₁ receptor antagonists such as AM251 to reduce the food intake and body weight of non-fasted and fasted 'non-obese' mice when administered once (Robinson et al., 2007) and of dietary-induced obese (DIO) mice when given repeatedly over 28 days (Cawthorne et al., 2007). Like AM251, THCV has also been found both to reduce the body fat content and plasma leptin concentration of DIO mice and to increase the 24h energy expenditure and thermic response to food of these animals (Cawthorne et al., 2007), the data obtained suggesting that THCV produces its anti-obesity effects more by increasing energy expenditure than by reducing food intake. In addition, both THCV and AM251 have been shown to reduce the time that 'non-obese' mice spend close to a food hopper (Robinson et al., 2007). It is also noteworthy that in contrast to rimonabant, THCV behaves as a CB₁ 'neutral' antagonist rather than as a CB₁ antagonist/inverse agonist. Still to be investigated is whether THCV ameliorates obesity and metabolic syndrome in man and whether, as proposed for rimonabant and other CB₁ receptor antagonists (reviewed in Le Foll and Goldberg, 2005), it might also be an effective medicine for the management of dependence on nicotine and/or other drugs. Results from *in vitro* experiments indicate that in addition to blocking CB₁ receptors, THCV activates CB₂ receptors (reviewed in Pertwee, 2007), prompting a need for experiments directed at establishing whether this plant cannabinoid also behaves as a CB₂ receptor agonist *in vivo*. Thus, a medicine that is both a CB₂ receptor agonist and a CB₁ receptor antagonist has potential for the management of certain disorders that include chronic liver diseases (reviewed in Mallat et al., 2007) and obesity associated with inflammation.

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SIGNS OF CANNABINOID CB₂ RECEPTOR ACTIVATION BY TETRAHYDROCANNABIVARIN, CANNABIGEROL AND CANNABIDIOL

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Introduction: The aim of this investigation was to characterize some of the pharmacological actions of two plant cannabinoids that have so far been the subject of very little research: cannabigerol (CBG) and Δ^9 -tetrahydrocannabivarin (THCV). Our experiments were directed at establishing first, whether CBG shares the ability of THC (Thomas *et al.*, 2005) to bind to mouse brain membranes and/or to CB₂ receptors at clinically-relevant (sub-micromolar) concentrations and second, whether either compound induces any detectable CB₂ receptor agonism as measured by inhibition of cyclic AMP production induced by 5 μ M forskolin in human CB₂-transfected Chinese Hamster Ovary (hCB₂-CHO) cells. CBG and THC were compared in some of these assays with the established CB₁/CB₂ agonist, CP55940, or with the plant cannabinoids, cannabidiol (CBD) and cannabigerolic acid (CBGA). The ability of THC to modulate [³⁵S]GTP γ S binding to hCB₂-CHO cell membranes was also investigated.

Methods: Our experiments were performed using methods described elsewhere (Ross *et al.*, 1999; Thomas *et al.*, 2007). CBD, CBG, CBGA and THC were obtained from GW Pharmaceuticals and all compounds were dissolved in dimethyl sulphoxide.

Results: We have shown previously that THC and CBD inhibit specific binding of [³H]CP55940 to hCB₂-CHO cell membranes with K_i values of 63 and 4200 nM respectively (Thomas *et al.*, 2005; 2007). In this investigation, the corresponding value for CBG was found to be 337 nM. CBG also displaced [³H]CP55940 from mouse whole brain membranes with a K_i value of 440 nM, the corresponding K_i values of CBD and THC being 4900 and 75 nM respectively (Thomas *et al.*, 2004; 2007). CBGA produced less than 50% displacement of [³H]CP55940 in both these binding assays, even at 10 μ M. At submicromolar concentrations, THC, CBD and CBG behaved as CB₂ receptor agonists as indicated by their inhibition of forskolin-induced stimulation of cyclic AMP production by hCB₂-CHO cells. Their rank orders of potency and intrinsic activity were CBD > THC > CBG and THC > CBG = CBD respectively. The intrinsic activity of each compound was less than that of CP55940. In contrast to CBD (Thomas *et al.* 2007), THC (0.01 nM to 10 μ M) did not produce any sign of inverse agonism in the [³⁵S]GTP γ S binding assay performed with hCB₂-CHO cell membranes.

Conclusions: Further research is required to establish whether THC also activates CB₂ receptors in vivo, and if so whether it displays anti-inflammatory and/or antinociceptive activity at clinically relevant doses. Thus, we recently showed that THC behaves as a CB₁ receptor antagonist in vivo (Pertwee *et al.*, 2007), and there are potential therapeutic applications for drugs that antagonize CB₁ receptors but activate CB₂ receptors. It will also be important to explore how CBD and CBG interact with CB₂ receptors in vivo and to establish whether CBG targets the CB₁ receptor as an agonist or antagonist.

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PHYTOCANNABINOID INDUCED ANOREXIC BEHAVIOUR IN FASTED AND NON-FASTED MICE

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Previous studies have revealed that the CB₁ antagonists SR141716A (Rimonabant), now approved by the FDA for clinical treatment, AM281 and AM251 reduce food intake and the consumption of palatable food. (-)- Δ^9 -tetrahydrocannabivarin (Δ^9 THCV) is a phytocannabinoid evident in cannabis. Recent work has shown that Δ^9 THCV behaves like a CB₁ antagonist *in vitro* and *in vivo*. In this study we therefore assessed whether Δ^9 THCV reduced food intake and appetite in both free-feeding and fasted mice and whether it could antagonise the hyperphagic effects of Δ^9 -tetrahydrocannabinol (Δ^9 THC). Moreover, we compared it with the synthetic CB₁ antagonist AM251.

Male C57BL/6 mice were used in all experiments. The drug groups tested were: AM251 (10 mg/kg), Δ^9 THCV-pure (3 mg/kg, 10 mg/kg or 30 mg/kg), Δ^9 THCV-rich Botanical Drug Substance (BDS) (containing 3 mg/kg, 10 mg/kg, 30 mg/kg THC) and vehicle. All drugs were administered intraperitoneally. In the food-deprivation study animals were deprived of food for 24 hours they were then weighed and injected with drug 1 hour before being placed in a cage where they were allowed to feed for 1 hour. Both food intake and weight gain were recorded. Phenotyper boxes were used to assess the feeding behaviour and overall activity of non-fasted mice with animals individually housed and subjected to a 12/12 hour light/dark cycle with free access to food and water. The Phenotyper is a video-based observation system which allows long-term continuous monitoring of behavioural activity on a normal circadian rhythm. The body weight of the mice, weights of food hoppers and water bottles were recorded each morning. Motor activity and time spent in the areas of the arena associated with food and water were also monitored 24 hours per day for three days prior to and 3 days following drug treatment. Drugs were administered 1 hour before the start of the night cycle.

AM251 reduced food intake and body weight in both fasted and non-fasted mice. In addition to the effects on feeding AM251 animals spent less time in an area associated with food retrieval and revealed a decrease in activity compared to controls. Similarly, animals treated with pure Δ^9 THCV displayed a reduction in body weight and food intake and spent less time in the food zone. By contrast, Δ^9 THCV-rich BDSs did not reduce body weight or food intake. However, since the BDSs also contained Δ^9 THC at doses known to induce feeding, Δ^9 THCV in the THC BDSs clearly antagonised the Δ^9 THC effect. Equivalent results were obtained in fasted animals.

Conclusions: The Phenotyper is a novel and valid method to assess feeding behaviour in non-fasted animals. Pure Δ^9 THCV has anorexic properties similar to those observed with AM251, and is even effective at very low doses. The lack of effect observed with the Δ^9 THCV BDS could be a result of the presence of Δ^9 -THC within it. Preliminary studies are being conducted to determine the effect of lower doses of Δ^9 -THCV BDS and therefore a reduced amount of Δ^9 -THC.

BEHAVIORAL EFFECTS OF CB2 CANNABINOID RECEPTOR ACTIVATION AND ITS INFLUENCE ON FOOD AND ALCOHOL CONSUMPTION

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Consumers of marijuana typically feel a strong compulsive desire to consume food. Although past research revealed that the CB1 cannabinoid receptor is a potent regulator of food intake, the functional presence of neuronal CB2 cannabinoid receptors in the brain had been controversial. The role of CB2 receptors in food and alcohol consumption and the behavioral effects of CB2 receptor ligands are not well understood. This is because CB2 cannabinoid receptors were thought to be absent from the brain and expressed primarily in immune cells and in the periphery. We tested the effects of peripheral injections of CB2 antagonist AM 630 CB2 agonist PEA and CB1 antagonist AM 251 on male C57BL/6, Balb/c, and DBA/2 mice at the beginning of the night cycle and after overnight 12-hour fasts. We also investigated the effects of the putative CB2 agonist, JWH015, and CB2 antagonist SR144528 in mouse motor function tests and in the two compartment black and white box were evaluated. Under standard conditions, the CB2 antagonist AM 630 inhibited food consumption of C57BL/6 mice and DBA/2 mice, but failed to block food intake of Balb/c mice. The CB2 agonist PEA had no significant effect on food consumption of Balb/c mice, and reduced food intake of C57BL/6 and DBA mice. The CB1 antagonist AM 251 inhibited food ingestion in the three mouse strains at variable times. After 12-hour food deprivation, the CB2 antagonist AM 630 increased food consumption C57BL/6 mice, but failed to produce significant changes in food intake for Balb/c and DBA/2 mice. The CB2 agonist PEA also reduced food consumption in all three mice strains at variable times. In comparison to the CB2 ligands, CB1 antagonist AM 251 inhibited food ingestion in the mouse strains. A general pattern of depression in locomotor activity was induced by JWH 015 in both males and females in the three mouse strains tested as the dose was increased. The development and enhancement of alcohol preference was observed following chronic treatment with CB2 agonist JWH 015 in stressed mice but not in controls. Using the DBA/2 strain the spontaneous locomotor activity and stereotype behavior was enhanced by acute administration of low doses of SR144528. There was a reduction in CNR2 gene expression in the ventral mid-brain region of mice that developed alcohol preference but not in those that did not develop alcohol preference. These effects of CB2 cannabinoid receptor ligands in *in vivo* behavioral tests are provided as functional evidence of CB2 cannabinoid receptors in the brain that plays a role in the modification of mouse behavior and in food and alcohol consumption of mice. Supported in part by CFR at WPUNJ and NIDA-NIH.

EFFECTS OF NON-PSYCHOACTIVE CANNABINOIDS ON PRECLINICAL AND CLINICAL PSYCHIATRIC/PSYCHOLOGICAL DISORDERS: A REVIEW AND RECOMMENDATIONS FOR FURTHER RESEARCH

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Introduction:

Recent evidence has revealed the potential therapeutic effects of constituents of the *cannabis* plant other than Δ^9 -tetrahydrocannabinol (THC), namely cannabidiol (CBD), cannabichrome (CBC) and cannibigerol (CBG). Each of these it at various stages of research progress.

Results:

CBD: There are both animal model and human research data that indicate that CBD has anxiolytic and anti-schizophrenic properties. There are substantial animal data that support the view that CBD has anxiolytic properties, namely on the conflict test, the Vogel test, the conditioned emotional response test, and the elevated plus maze test. In human research, in healthy volunteers, CBD reduces feelings of anxiety, psychotic symptoms, and feelings of cannabis intoxication. CBD also reduces anxiety induced by a public speaking test. Finally, CBD reduces anxiety during a regional cerebral blood flow test (rCBF) test and increases activity on the rCBF scan in the left parahippocampal gyrus. In regard to other anxiety disorders, there is some data that CBD might reduce symptoms in bipolar disorder. In regard to Schizophrenia, there is one small of N=1 patients that indicates CBD may reduce symptoms and furthermore a double-blind study revealed that CBD reduced symptoms of acute psychosis but this study clearly needs replication and extension.

CBC: There is evidence that CBC has antidepressant properties in animal models of depression. In addition, it blocks the anxiogenic effect of THC administered in a high dose in animals.

CBG: There is also evidence that CBG has antidepressant properties in an animal model of depression.

Conclusions:

Taken together, these data suggest that much more research should be conducted on these *cannabis* constituents.

Research problems with these *cannabis* compounds include bioavailability, route and type of administration, as well as the the formulation, pure compounds vs. extracts. Significant collaboration should occur to advance this potential therapeutic work.

BEYOND THC: THE COMPLEMENTARY THERAPEUTIC ROLE OF MINOR PHYTOCANNABINOIDS, TERPENOIDS AND FLAVONOIDS

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Introduction: Since its formal discovery and synthesis in 1964, THC has been the pre-eminent focus of research into both therapeutic and adverse effects of cannabis. In recent times, however, increasing interest has developed in complementary effects of minor phytocannabinoids (CBD, CBG, CBC, THCV and other propyl series components), cannabis terpenoids and flavonoids (see McPartland-Russo, *Journal of Cannabis Therapeutics* 2001; 1(3-4):103-132 for earlier review). The current presentation will focus on newer data for these agents and future targets for research.

Methods: The PubMed/NLM database was reviewed for numerous pertinent keywords. The author's extensive library of books and older articles were also examined for additional material. Particular focus was placed on research of the last several years, and that done on agents not addressed in previous publications, especially the cannabis terpenoids, such as nerolidol, caryophyllene oxide, and phytol.

Results: CBD displays myriad activities as an anti-anxiety, antioxidant, analgesic, cytotoxic agent, etc. (Russo-Guy, *Medical Hypotheses* 2006; 66(2): 234-46), with recent evidence that it also may prevent delayed vomiting in chemotherapy, is anti-inflammatory by increasing adenosine signaling via inhibition of its uptake, limits endothelial, retinal and islet cell damage in diabetes, and β -amyloid damage in Alzheimer disease. CBC and CBG have shown promise in animal models of anxiety and depression, while the latter has also demonstrated cytotoxic properties in various cancer cell lines, and prominent antihypertensive activity. THCV shows great promise as an anorectic agent and anticonvulsant. Cannabis terpenoids show promise as modulators of THC function to reduce memory impairment, boost analgesia via complementary mechanisms, etc. Phytol produces sedative effects, and counters teratogenesis produced by retinoids. Nerolidol may increase skin penetration of topical medicines, and produce antiparasitic effects in leishmaniasis and malaria. Caryophyllene oxide is a potent antifungal agent and antibiotic against *Proteus mirabilis*, a common urinary tract pathogen. Data will be presented to support the premise that even tiny concentrations of these agents may be sufficient to produce important pathophysiological benefits. Experiments are planned to assess cannabinoid-terpenoid interactions in the CNS pertinent to anxiety, depression and other processes.

Conclusion: Minor phytocannabinoids, cannabis terpenoids and flavonoids produce an entourage effect that may offer important contributions to enhance benefits of and reduce adverse events attributable to THC.

UGT 1A3 AND 1A1 ARE THE TWO MAIN HUMAN RECOMBINANT UDP-GLUCURONOSYLTRANSFERASE ISOFORMS RESPONSIBLE FOR THE GLUCURONIDATION OF (-)-11-NOR-9-CARBOXY-DELTA-9-TETRAHYDROCANNABINOL *IN VITRO*

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11-nor-9-carboxy-*delta*-9-Tetrahydrocannabinol (THC-COOH) and its glucuronide ester conjugate are the major end products of *delta*-9-Tetrahydrocannabinol (THC) metabolism. These metabolites are mainly produced in the liver, extensively bound to proteins, more water-soluble than their parent compounds and excreted into bile and urine. Generally, glucuronidation is considered as a detoxification mechanism. However, isomerisation of the glucuronide conjugate has been reported. These isomers may be able to bind irreversibly to plasma proteins forming potentially toxic adducts. UGT enzymes are responsible for the conjugation of THC-COOH, they belong to two UGT 1A and 2B families, each with several isoforms. UGT activity changes by induction, inhibition and genetic variability may have serious clinical consequences. Nothing is known about the human UGT isoforms involved in THC-COOH glucuronidation. The goal of this study was to identify the UGTs isoforms responsible for THC-COOH glucuronidation *in vitro* and to determine their kinetic parameters. These values were also compared to the *postmortem* concentrations of THC-COOH in the liver. To test the ability of various UGTs to form THC-COOH glucuronide, *in vitro* incubations were performed with human cDNA expressed UGT isoforms 1A1, 1A3, 1A4, 1A6, 1A7, 1A8, 1A9, 2B4, 2B7, 2B15 and 2B17. The enzymes were incubated with MgCl₂, a pore forming protein (alamethicin), uridine diphosphoglucuronic acid (UDPGA) and THC-COOH at various concentrations (25-400 μM) for different time-periods. Because no THC-COOH-glucuronide reference standard is commercially available, enzymatic conjugation rates were expressed as area ratios of THC-COOH-glucuronide to THC-COOH-d₉ as determined by TurboIonSpray LC-MS operating in the negative mode. Liver concentrations of free and total THC-COOH were determined by GC-MS. Results show that UGT1A3 and 1A1 and to a lesser extent UGT 1A9 and 2B4 are the most active. Using Michaelis-Menten kinetics, K_m values were of 90 and 88 μM for UGT 1A3 and 1A1, respectively, suggesting a low affinity for THC-COOH. These K_m values are also very high when compared to those reported for cytochromes P450 2C9/2C19 (2.1 and 3.8 μM, respectively). CYP 2C9/2C19 are involved in the oxidation of THC into THC-COOH. The K_m values determined for UGTs 1A3 and 1A1 are also much higher than typical hepatic concentrations measured *postmortem* in human (THC-COOH: ~ 0.05 μM and THC-COOH-glucuronide: ~ 0.35 μM). The functional and clinical relevance (such as in the case of Gilbert's syndrome) of THC-COOH glucuronidation by various UGT isoforms will be discussed.

ACUTE EFFECTS OF Δ^9 -TETRAHYDROCANNABINOL AND STANDARDIZED CANNABIS EXTRACT ON THE AUDITORY EVOKED MISMATCH NEGATIVITY

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Δ^9 -Tetrahydrocannabinol (Δ^9 -THC) and Cannabidiol (CBD) are the two major constituents of *Cannabis sativa* showing contrary effects. Administration of Δ^9 -THC as an agonist at the central cannabinoid receptor (CB₁) to normal subjects may induce psychotic reactions with hallucinations, delusions, depersonalization and emotional lability as well as cognitive deficits closely resembling schizophrenia. 11-OH-Tetrahydrocannabinol (11-OH-THC) is the most important psychoactive metabolite of Δ^9 -THC that shows a similar spectrum of actions. In contrast, CBD as a CB₁-antagonist seems to possess neuroprotective and antipsychotic activity. 11-nor-9-carboxy-Tetrahydrocannabinol (THC-COOH) is the most important non-psychoactive metabolite of Δ^9 -THC. Nowadays, a close relationship between cannabis, the endocannabinoid and dopaminergic system, and the onset of schizophrenic psychosis is discussed.

The mismatch negativity (MMN) is a negative component of the auditory event-related brain potential reflecting auditory sensory memory and auditory information processing. Reduced MMN amplitudes were often found in patients with schizophrenia. We used this established model to study the biological mechanisms of cannabis-induced psychotic states and schizophrenic conditions by comparing Δ^9 -THC and standardized cannabis extract, that principally contains Δ^9 -THC and CBD, in normal subjects.

Methods: This prospective, double-blind, placebo-controlled cross-over study investigated the effects of Δ^9 -THC and standardized cannabis extract containing Δ^9 -THC and CBD on MMN amplitude in 22 healthy volunteers (age 28 ± 6 years, 11 male). The MMNs resulting from 1000 auditory stimuli were recorded by 32 channel EEG. The standard stimuli (90%) were 1000 Hz, 80 dB SPL, 100 ms duration, the deviant stimuli (10%) differed in frequency (1500 Hz). After the MMN recordings, blood samples were taken and controlled for Δ^9 -THC, its metabolites 11-OH-THC and THC-COOH, and CBD.

Results: 1.) Significantly greater MMN amplitude values at Cz, C3 and C4 were found under cannabis extract, but not under Δ^9 -THC, in comparison to placebo. There were no significant differences between MMN amplitudes at frontal electrodes. **2.)** A significant correlation was found between the 11-OH-THC plasma concentration and MMN amplitude at central electrodes showing smaller amplitudes with higher concentrations. Plasma concentrations of Δ^9 -THC, THC-COOH and CBD were not significantly correlated with the MMN amplitude.

Conclusions: 1.) Since the main difference between Δ^9 -THC and standardized cannabis extract is CBD, it can be speculated whether the greater MMN amplitude which implies higher cortical activation and cognitive performance is related to the positive effects of CBD, contributing to the hypothesis of the antipsychotic effect of CBD. This effect may be relevant for auditory cortex activity in particular because only MMN amplitudes at the central, but not at the frontal electrodes were enhanced under cannabis extract. **2.)** It can be suggested that the negative correlation mentioned above is based upon the influence of 11-OH-THC as a CB₁ agonist on the endogenous cannabinoid system interacting with the dopaminergic system. Otherwise, the plasma concentrations of 11-OH-THC that were measured at the end of the experiment may reflect those of Δ^9 -THC during the experiment.

CANNABIS TEA REVISITED: A SYSTEMATIC EVALUATION OF THE CANNABINOID COMPOSITION OF CANNABIS TEA

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A significant part of medicinal users consume cannabis in the form of a tea. In The Netherlands, it is advised by the Office of Medicinal Cannabis to prepare cannabis tea by boiling 1 gram of cannabis in 1 L water for 15 minutes (=standard protocol). However, not much is known about the composition of cannabis tea, or the effect of different parameters during preparation, handling or storage. In this study we used the high-grade medicinal cannabis available in Dutch pharmacies to study the cannabinoid composition of tea under standardized and quantitative conditions.

Methods: Tea, prepared according to the standard protocol, was used as the reference material during this study. Subsequently, experimental conditions were systematically varied in order to mimic the possible variations made by medicinal users. These included: volume of tea prepared; boiling time; amount of cannabis used; and storage time in a refrigerator. To improve the solubility of cannabinoids during refrigerated storage, the effect of added solubilizers (coffeecreamer and cyclodextrin) was evaluated. During analysis there was a specific focus on the cannabinoids tetrahydrocannabinol (THC) and its acidic precursor, tetrahydrocannabinolic acid (THCA). Quantitative analysis was performed by HPLC and NMR.

Results: This study clearly shows the effect of varied parameters on the cannabinoid composition of cannabis tea. Because of the relatively low temperature involved (boiling water), the conversion of THCA into THC was limited. The composition of tea, prepared according to the standard protocol was very reproducible. Cold storage of tea resulted in fast precipitation of cannabinoids, but this could be greatly improved by addition of solubilizers.

Conclusion: Cannabis tea prepared under standardized conditions can be a reproducible administration form, but because of the low aqueous solubility of cannabinoids, it has limited potency. The obtained results provide a clear quantitative insight into the biochemistry of cannabis tea preparation, and will contribute to a better appreciation of this convenient mode of cannabis administration.

**REGULATING COMPASSION;
AN OVERVIEW OF CANADA'S
FEDERAL MEDICINAL CANNABIS POLICY AND PRACTICE**

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Background: In response to a number of court challenges brought forth by Canadian patients who demonstrated that they benefited from the use of medicinal cannabis but remained vulnerable to arrest and persecution as a result of its status as a controlled substance, in 1999 Canada became the second nation in the world to initiate a centralized medicinal cannabis program. Over its six years of existence, this controversial program has been found unconstitutional by a number of courts, and has faced criticism from the medical establishment, law enforcement, as well as the patient/participants themselves.

Methodology: This critical policy analysis is an evidence-based review of court decisions, government records, relevant studies and recent Access to Information Act data related to the three main facets of Health Canada's medicinal cannabis policy - the Marihuana Medical Access Division; the Canadians Institute of Health Research Medical Marijuana Research Program; and the Prairie Plant Systems cannabis production facility - as well as the nation's main suppliers of therapeutic cannabis, Canada's network of unregulated compassion clubs and societies.

Results: There is a growing body of evidence that Health Canada's program is not meeting the needs of Canada's medical cannabis patient community and that the policies of the Marihuana Medical Access Division may be significantly limiting the potential individual and public health benefits achievable through the timely and effective therapeutic use of cannabis by critically and chronically ill Canadians.

Conclusion: Any future success of this federal program will depend on the government's ability to better assess and address the concerns and needs of the nation's critically and chronically ill, to promote and fund an expanded clinical research agenda, and to work in cooperation with Canada's established network of community-based medicinal cannabis compassion clubs and societies.

Lucas, P. (2007). *International Journal of Drug Policy*; in press.

PRESENCE AND FUTURE OF LEGAL MEDICINAL CANNABIS IN THE NETHERLANDS

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At the end of the 20th century the Dutch government decided that medicinal cannabis should be available for scientific research and in pharmacies as a prescription medicine. According to the Single Convention on Narcotic Drugs, 1961 (and amended in 1972) a government taking this approach needs to fulfil certain obligations. It is obliged to install a national bureau that acts as wholesaler and commissions third parties to cultivate cannabis, to perform quality control and packaging and other logistical tasks. To elaborate practical measures a bureau was installed at the Ministry (the Office for Medicinal Cannabis - OMC) in 2000. In 2003 OMC makes medicinal cannabis available for patients on prescription. OMC stimulated research with medicinal cannabis and made information available to patients and professionals (national and international).

In spite of the efforts described the number of patients obtaining medicinal cannabis on prescription has turned out to be much lower than expected. The main reasons for this was the high price and the fact that medicinal cannabis was not reimbursed by health insurers.

In 2005 the policy on medicinal cannabis was evaluated. The decision was made to continue the established policy. However the focus of the OMC changes. In cooperation with scientists and other partners the OMC increases communication with the aim to change the general opinion on cannabis as a medicine. For instance presentations and workshops were given at meetings for patients(organisations), physicians and pharmacists. Secondly, a pilot experiment was started to make cannabis available on prescription for a price which is comparable or even lower than the price of cannabis in the Dutch coffeeshop. This pilot is executed with a pharmacy which specializes in dispensing medicinal cannabis.

Thirdly the Office focuses on product development. A new cannabis variety called Bediol became available on prescription which has a dronabinol/cannabidiol concentration of ca. 6 and ca. 8% respectively. A registered pharmaceutical product with cannabis as starting material will be developed by a consortium of Dutch companies. The business plans are ready and will be carried out the coming years.

And last but not least the Office established contacts with associations of patients and health authorities in other (European) countries in an attempt to make cannabis available on prescription.

ENDOCANNABINOID-MEDIATED RETROGRADE SIGNAL TRANSMISSION BETWEEN NEURONS

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Anatomical and functional studies have shown that CB₁ cannabinoid receptors are ubiquitously distributed in the central nervous system and that they are preferentially localized on presynaptic axon terminals, where their activation leads to inhibition of neurotransmitter release from the terminals. However, the physiological role of the CB₁ receptors was, at first, not known. This was changed by the discovery of the roles of endocannabinoids and CB₁ receptors in retrograde synaptic signaling. During usual synaptic transmission (orthograde transmission), the presynaptic axon terminal releases neurotransmitter and the neurotransmitter affects the function of the postsynaptic neuron. The opposite occurs during retrograde synaptic transmission: a signaling molecule released by the postsynaptic neuron affects the function of the presynaptic axon terminal. Endocannabinoids are frequently the signaling molecules during retrograde signaling (see Figure 1), and endocannabinoid-mediated retrograde signaling is the basis of several forms of short- and long-term synaptic plasticity.

It has been shown that endocannabinoids are involved in the short-term (lasting from milliseconds to 3 minutes) plasticity of glutamatergic and GABAergic synapses in the cerebellum, ventral tegmental area, hippocampus, caudate-putamen, amygdala and cortex. Endocannabinoids are also involved in long-term (lasting more than 20 minutes) plasticity of synapses in the amygdala, nucleus accumbens, hippocampus, caudate-putamen and cortex.

Much effort has been undertaken to determine the chemical identity of the released endocannabinoid. Inhibition of the 2-arachidonoylglycerol-producing enzyme diacylglycerol lipase abolished retrograde signaling in most brain regions. In contrast, inhibition of the 2-arachidonoylglycerol-degrading enzyme monoglyceride lipase potentiated retrograde signaling. Thus, it is very likely that 2-arachidonoylglycerol is more important for retrograde signaling than the other major endocannabinoid, anandamide.

The therapeutic possibilities and consequences arising from the operation of endocannabinoid-mediated synaptic plasticity are manifold. On the one hand, it is possible to deliberately influence synaptic plasticity, and thus memory and learning processes, by modulating endocannabinoid production and degradation. On the other hand, activation or blockade of CB₁ receptors for other purposes (for example, for analgesia and appetite reduction) may lead to unwanted interference with endocannabinoid-mediated memory and learning processes.

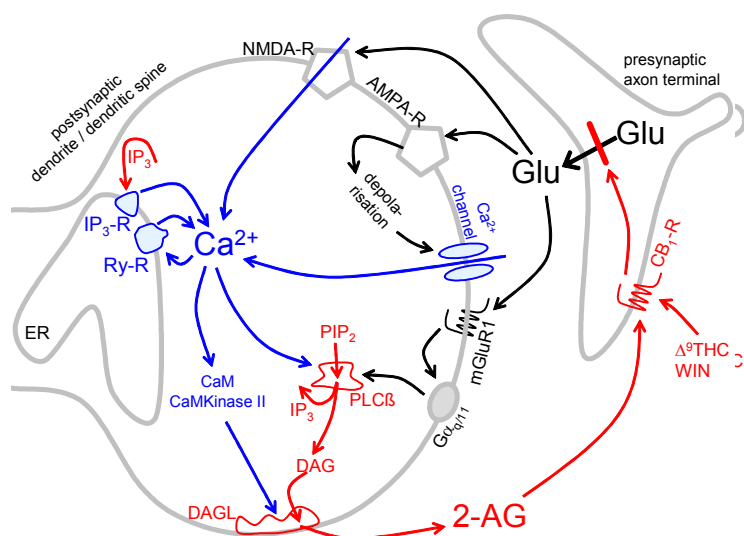


Figure 1. Endocannabinoid-mediated retrograde signaling. Two major triggers can elicit 2-arachidonoylglycerol (2-AG) production in a postsynaptic neuron: an increase in intracellular calcium concentration and activation of G $\alpha_{q/11}$ protein-coupled receptors. Calcium flows into the neuron via voltage-gated calcium channels opened by the depolarizing glutamatergic synaptic input. Glutamate also activates G $\alpha_{q/11}$ protein-coupled metabotropic mGluR1 receptors.

CANNABIS CONSUMPTION AND DRIVER FITNESS

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The assessment of drug users' fitness to drive became one of the most important issues within the current road safety related political discussion in Germany.. On the basis of zero tolerance legislation the key committee, responsible for the standardisation of the respective assessment procedures, inter alia deals with the determination of analytical thresholds for different types of drugs. Beside defining an analytical threshold for THC the German Driving License Regulations stipulates that the consumption pattern as well as the ability to sort consumption of Cannabis out from driving has to be taken into account.

The objective target of the present study on road safety related consequences of cannabis consumption was the evaluation of potential and actual hazards in road traffic concerning driving abilities.

In the first part of the investigation a detailed literature survey was performed considering the neuropsychological and psychiatric effects of cannabis use. The survey especially dealt with the degree of evidence for impairment by weighting the quality of the available studies. The largest number of consistently impaired behavioral functions was found for the consumer setting of an "occasional user after acute consumption". Neither consistent impairments were found for the abstinent occasional consumers nor in the residual phase. There was no consistent evidence found for more severe impairments of behavioral functions in heavy cannabis users, neither acutely nor during abstinence.

The results of the literature survey lead to the conclusion - that the differentiation of Cannabis consumption patterns is not reasonable for the assessment of driver's fitness are.

In the second part of the study data from persons which were tested cannabinoid-positive following a deviant driving performance during 3 years (2000-2002) were evaluated with respect to their actual cannabinoid concentrations in the plasma. In doing so the relationship between THC and THC-metabolite concentrations in the plasma and the behavioral impairment scored by police officers and physicians was investigated. Neither the evaluation of the police nor of the physicians was confounded with THC or 11-OH-THC values in serum.

These results prove that neither the behavioral scoring by police nor by physicians are suitable for both, to reflect psychotomimetic and other Cannabis actions effectively or to differentiate between occasional and heavy cannabis consumption with an acceptable degree of certainty.

DEVELOPING LIMITS FOR DRIVING UNDER THE INFLUENCE OF CANNABIS

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Objective: Development of a rational and enforceable basis for controlling the impact of cannabis use on traffic safety.

Methods: An international working group of experts on issues related to drug use and traffic safety evaluated evidence from experimental and epidemiological research and discussed potential approaches to developing per se limits for cannabis.

Results: In analogy to alcohol, finite (non-zero) per se limits for THC in blood appear to be the most effective approach to separating drivers who are impaired by cannabis use from those who are no longer under the influence. Limited epidemiological studies indicate that serum concentrations of THC below 10 ng/mL are not associated with an elevated accident risk. A comparison of meta-analyses of experimental studies on the impairment of driving-relevant skills by alcohol or cannabis suggests that a THC concentration in the serum of 7-10 ng/mL is correlated with an impairment comparable to that caused by a blood alcohol concentration (BAC) of 0.05 percent. Thus, a suitable numerical limit for THC in serum may fall in that range.

Conclusions: This analysis offers an empirical basis for a per se limit for THC that allows identification of drivers impaired by cannabis. The limited epidemiological data render this limit preliminary.

FARMING AND PROCESSING OF INDUSTRIAL HEMP: AN OVERVIEW OF 12 YEARS OF PRACTICAL EXPERIENCE

Bernd Frank, Managing Director, BaFa GmbH, Malsch, Germany

BaFa GmbH is Germany's first and most established processor of industrial hemp. Since 1996, the company has contracted with farmers for the production of hemp stalks and, more recently, hemp seeds. At its Malsch plant, BaFa processes the stalks into fiber for automotive composites and insulation materials and into hurds (shive) for horse bedding and building materials. The presentation briefly reviews key issues on farming and processing of hemp, including: farm selection, choice of hemp variety and planting seeds, field preparation, planting, field maintenance, harvesting for fiber and seeds and primary processing.

BASIC GUIDELINES FOR THE CULTIVATION OF CANNABIS SATIVA FOR MEDICINAL AND PHARMACEUTICAL PURPOSES.

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When using cannabis flos (dried female flowers of the plant cannabis Sativa) as a medicine the next two things need to be fully clear to prescribers and end-users.

1.1 The composition with regard to content of the plant (cannabinoids and other endogenous substances such as terpenes) must be stable. Both within one batch and also within several batches of the same plant variety.

1.2 Sterility of cannabis flos must be guaranteed just as being not contaminated by (residue of) pesticides, heavy metal and remaining not endogenous material (dead insects, bacteria, moulds).

The grower and supplier of medicinal cannabis are responsible for undesirable deviations in these two requirements.

Ofcourse there are more aspects to assure a reliable deliverance of medicinal cannabis, such as

2.1 Reliability of product and supply. Can be assured through external control on composition of the different products; and proven batchquantity.

2.2 Reliability of the growingcompany in genereral. Existance of a backup on all plant material and measures to reduce the risk of contamination when new plantmaterial is introduced.

2.3 security aspects, both internally (reliable personal) and externally (anti burgling system).

Concerning 1.1 and 1.2

Garantees on a stable composition of cannabis with regard to content of plantsubstances (cannabinoids as the most desired ones) is primarily based on maintaining the genetic code of the plant and standardisation of some (proven) cultivation - and processing circumstances. Such as:

1. Cloningtechnique (to maintain the genetic code)
2. Selection of plants
3. Conserving (harvesting and drying)
4. Processing (manicuring, grinding).

Critical parameters for external appearance and sterility of the product and a standardised and reliable turn over are:

1. Standardisation of regulable parameters in the cultivation such as: use of isolated (temperature and light) areas to grow and fixed schedules for several routines
2. Strict protocols on maintaining hygienic circumstances in the whole growing and processing areas.
3. Avoiding contamination of cannabis flos by pesticides, fungicides, predators or heavy metals
4. Gamma-irradiation of the final product.

Conclusion

It is very well possible to grow and process cannabis sativa for the production of cannabis flos for medical use, in a standardised way as well within one batch as in several batches over years, without visible or measurable loss of quality and a stable content of cannabinoids. So searching for a reliable source of cannabis for both, scientific purposes and/or prescription to patients is no longer needed.

OPTIMIZATION OF AGRO-TECHNIQUES OF HEMP (*Cannabis sativa* L.) FOR PHARMACEUTICAL APPLICATIONS

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The genus *Cannabis* is composed of several chemotypes which variously produce amounts of particular cannabinoids, terpenoids and other molecules. When growing herbal drugs the method of cultivation, harvesting and primary processing of the plant determine the ultimate properties of the active pharmaceutical principles. As a result, the entire production process needs to be standardized.

Production of high-grade medicinal *Cannabis* can be realized all year long in a greenhouse or indoors. In order to guarantee the quality of the final product, it is important to follow the guidelines for Good Agricultural Practice of the European Medicines Evaluation Agency. Growing *Cannabis* usually requires a government license. Choosing the right cultivation method is important to maximize the production of active principles, to improve the quality of the raw material and to ultimately decrease production costs. We performed two trials evaluating the effects on yield, total cannabinoid and terpenoid content while using four different cultivation methods, based on specific substrates and fertilizers. We grew CBD (cannabidiol) and CBG (cannabigerol) chemotypes, previously selected from hemp cultivars, to determine the variation of cannabinoid content in the leaves and inflorescences during and at the end of the cultivation cycle.

Methods: 20 inbred lines (200 plants in total - 50 per treatment) were used in trial 1, whereas 2 clonal progenies (68 plants in total - 17 per treatment) were used in trial 2. The plants were grown in two different greenhouses and during two different seasons. We tested 3 different types of substrates and 4 different types of fertilizers, one of which was certified for organic farming. After the assessment of the biometric parameters, cannabinoid and terpenoid content were evaluated by means of gas chromatographic analysis.

Results: In the first trial we found a chemotypical variation between the examined 20 inbred lines and we selected the ones with the highest CBD or CBG total yield. The lines showed a constant response to the various applied treatments. In the second trial, the highest content of cannabinoids (expressed as a percentage of dry matter) was obtained with treatments characterized by a limited amount of fertilizing elements. These same treatments were also characterized by a low production of plant leaves and inflorescences. The highest cannabinoid and terpenoid content (expressed as grams per plant) was obtained with treatments T3 and T4, characterized by the same substrate but by two different types of fertilizer (mineral vs. organic). The comparison between these treatments shows that CBD, CBG and terpenoid production (grams per plant) does not vary significantly ($p \leq 0.05$). We showed a correlation between the content percentage of cannabinoids and total yield with the production of plant inflorescences. The results also show a gradual decrease of cannabinoid content in the leaves as the reproduction stage starts to become longer than the optimal maturation stage.

Conclusion: These results confirm the known relationship between the cultivation method and the production of active principles in medicinal plants. Adopting the most appropriate cultivation method can improve quality, sustainability, efficiency and yield of *Cannabis* production for pharmaceutical applications.

Posters

CYSTIC FIBROSIS: INFERTILITY AND DECREASED MOTOR ACTIVITY MAY BE PREVENTED BY THC TREATMENT DURING DEVELOPMENT

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Introduction: Cystic fibrosis (CF) is an inherited disease accompanied by several physiological impairments, including infertility and decreased motor activity. An impairment in fatty acid balance was proposed as a major factor in CF etiology, we therefore hypothesized that the balance of *endocannabinoids* (which are derivatives of fatty acids) may be impaired in CF. On this basis, we have examined behavioral parameters, weight gain and fertility in CF mice, as well as the possibility of their improvement by Δ^9 -tetrahydrocannabinol, THC (the major component of the marijuana plant) treatment.

Methods: The study was performed on a mouse model for cystic fibrosis (*cftr*^{-/-}, cystic fibrosis transmembrane conductance regulator-deficient mice). Wild type mice (*cftr*^{+/+}) were used as controls. CF and control mice were treated in infancy with Δ^9 -THC, 5 mg/kg of THC or with vehicle, daily for 3 weeks, from day 8 until 28. During the first month of life body weight gain was recorded. At adulthood, at the age of 9-10 weeks, motor behavior was tested in an open field and anxiety-related behavior was measured in the elevated plus maze. Fertility was assessed as the number of litters born to one female over a 6 month period. CB1 receptor densities were assessed in tissue of CF and control mice

Results: THC treatment significantly decreased weight gain in CF males (during treatment), while females showed weight increase. CF adult mice (males) displayed significantly decreased motor activity and increased anxiety levels compared to *wild type* animals. These impairments were prevented in CF mice treated with THC during development. All studied CF males (n=3) and females (n=3) were infertile, while CF males (n=2) and females (n=4) which were treated with THC during infancy, showed fertility comparable to that of wild type animals. Male CF mice had significantly lower receptor densities than healthy males.

Conclusions: These data suggest that reproduction, motor and emotional behavior is impaired in CF mice, and that THC treatment during development leads to functional improvement in behavior and fertility. Further evidence for an interaction between *cftr* and CB1 receptors is provided by the lower CB1 receptor densities in CF mice. Sex differences should be taken into account when studying the putative interaction between *cftr* and CB1 receptors. We are currently investigating CB1 receptor expression in brain and reproductive organs of CF mice.

SOURCE DIFFERENTIATION OF THC BY GC/MS PROFILING

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Background: There is increasing evidence for the therapeutic benefits of delta-9-tetrahydrocannabinol (THC, dronabinol) in the treatment of spasticity, nausea, appetite loss, pain, etc. The only THC-based, approved drug is Marinol® (encapsulated synthetic THC). However, its major drawbacks are cost and limited market availability. In addition, oral formulations are characterized by low bioavailability. Therefore, THC of alternative sources and manufacturers is required for pharmacological, pharmaceutical and clinical research as well as prescription. In Switzerland, the current narcotic law does not allow the use of Cannabis-derived or semi-synthetic THC outside of research projects. Consequently, for regulatory authorities, analytical proof of the THC source by using chemical markers is mandatory in a therapeutic context.

Methods: Semi-synthetic and synthetic THC was prepared by THC-Pharm following GMP procedures. Natural THC was isolated from THC-rich *Cannabis* plants and purified by column chromatography and medium pressure liquid chromatography (MPLC). Gas chromatography/mass spectrometry (GC/MS) was used for THC profiling. The markers were identified by their mass spectra (full scan) and by comparing with synthesized standards. Selected ion monitoring (SIM) enables the detection of even trace-amounts of these markers.

Results: Fully-synthetic THC (THC-Pharm, purity >98%) is characterized by its content of ethyl-THC (THC-C2). Semi-synthetic THC (THC-Pharm, >99%), produced by cyclization of natural cannabidiol (CBD), contains the markers butyl-THC (THC-C4) and propyl-THC (THC-C3; THCV); THC-C2 is not present. Natural (biogenic) THC, isolated from *Cannabis* plants of various origin, and with a purity of >95%, can be identified by cannabichromene (CBC) and CBD. However, the latter cannabinoid is usually also present in fully-synthetic THC, where synthetic CBD is the starting material. Synthetic and semi-synthetic THC contain both delta-8-iso-THC, which can be easily misinterpreted as CBC.

Conclusions: The presence or absence of non-biogenic and biogenic chemical markers, such as THC homologues, CBC or CBD, allows an unequivocal differentiation of the production method of high-purity THC. GC/MS-SIM is needed to detect the trace amounts of these cannabinoid-type markers.

PHARMACOKINETICS AND ADVERSE EFFECTS OF PULMONAL AND INTRAVENOUS THC-CBD FORMULATIONS

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Background: Due to variable absorption and extensive first-pass metabolism, the bioavailability of oral (p.o.) delta-9-tetrahydrocannabinol (THC) is low (5-20%) and therefore alternative application forms are necessary. In a previous study (Naef M. et al. J. Pharm. Sci. 2004;93:1176-84) we could show an increased bioavailability (29%) after inhalation (i.h.) of a THC aerosol by using a pressure-driven inhalator (Pari Master). The tolerability of the aqueous, nebulised aerosol was good but significant cough and irritation of the upper airways were seen influencing the efficiency of the inhalation process and the resulting bioavailability.

Methods: In a subsequent open-label, 2-period study on 12 healthy volunteers a combination of THC and cannabidiol (CBD) was compared i.h. and intravenously (i.v.). The liquid aerosol was produced by an in-vitro validated pMDI device, releasing about 45% of the cannabinoid dose, enabling a dosage of about 90 µg THC and 90 µg CBD per actuation. Three subjects (pilot study) received 360 and 9 subjects 720 µg THC-CBD, corresponding to 4 and 8 actuations, respectively. The addition of a local anaesthetic to the pulmonal preparation should prevent mucosa irritation and coughing. The pharmacokinetic evaluation was based on plasma profiles acquired by GC/MS. Adverse effects were monitored by visual analog scales (VAS) and measuring vital functions.

Results: After 360-µg i.h. and i.v. doses, THC and CBD were not measurable in plasma longer than 20 min after administration, therefore only plasma levels resulting after 720 µg were further evaluated. After i.h. and i.v. administration, THC plasma peaks were observed 5 min post-drug, with THC peak concentrations from 3 to 22 and 13 to 40 ng/ml, respectively. CBD peaks, with concentrations from 2 to 17 and 14 to 26 ng/ml, were also measured after 5 min. The elimination half-lives were 7 (THC) and 11 min (CBD) after i.h., 22 and 24 min after i.v. administration. The mean i.h. bioavailability (calculated vs. i.v.) was 55 ± 37 and 59 ± 47 % for THC and CBD, respectively. This represents a 2-fold increase compared to the previous study. After i.h., the THC metabolism was less pronounced than after p.o. administration. Conjugated 11-carboxy-THC was the main metabolite. The aerosol was generally well tolerated with little or no coughing, and only slight psychotropic side-effects were observed in some subjects. These were more distinct after i.v., especially irritations and hallucinations. Besides moderate tachycardia, the vital functions stayed unchanged.

Conclusions: We conclude that a THC-CBD i.h. aerosol shows favorable pharmacokinetic properties, which are similar to those of an i.v. preparation. Adding a local anesthetic is recommended to prevent coughing. The negligible psychoactivity may result from the antipsychotic CBD, the low THC dosage and/or the decreased formation of the psychoactive metabolite 11-hydroxy-THC. Therefore, the inhalation via pMDI is an alternative to the p.o. administration route and is an option for reliable and safe application of cannabinoids in a clinical context.

CANNABINOID ACTION IN THE OLFACTORY EPITHELIUM

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Sensory olfactory information is crucial in several behavioral aspects of humans and animals, e.g., nutrition and reproduction. For example in mitral cells of the rat olfactory bulb, the responsiveness to food odors depends on the nutritious status of the animal. Some modulation may even occur in the olfactory epithelium (OE). In hungry axolotls s-neuropeptide Y enhances EOG responses to L-glutamic acid and modulates the amplitude of a tetrodotoxin-sensitive inward current.

Recently, the endocannabinergic system (ECS) has also been shown to be involved in food intake and energy homeostasis. Because in different animal phyla the levels of endocannabinoids are increased under fasting conditions, endocannabinoids may act as orexigenic mediators. These observations, together with the role of olfaction in food detection, led us to investigate whether olfactory receptor neurons (ORNs) are modulated by the cannabinergic system, which clearly turned out to be the case.

Methods: Responsiveness of olfactory neurons to odours were measured using the patch clamp technique in on-cell configuration and high resolution confocal calcium imaging using Fluo4 as calcium indicator. To investigate any modulation of the induced spatiotemporal activity pattern the preparation was incubated with the CB1-receptor specific antagonists AM251, AM281, LY320135 or the CB1 specific agonist HU210. To localize the CB1 receptors a detailed immunohistochemistry using a rat CB1-NH antibody (generous gift from Ken Mackie) was carried out.

Results: First, we show that CB1 receptor-specific antagonists AM251, AM281, and LY320135 decrease and delay odour-evoked calcium changes in olfactory receptor neurons. Second, we localize CB1-like immunoreactivity on dendrites of olfactory receptor neurons. Finally, we describe the cannabinergic influence on odour-induced spike-associated currents in individual olfactory receptor neurons.

Conclusions: We demonstrate for the first time that the cannabinergic system has a profound impact on peripheral odour processing. Recently, several studies have been published dealing with the influence of the nutritious status on the neurophysiology of olfactory information processing and vice versa, whereby some of the phenomena could indirectly be attributed to the effects of modulators like orexin in the rat olfactory bulb or s-neuropeptide Y in the OE. The ECS is also involved in food intake and energy homeostasis. For instance, in the teleost fish *Carassius auratus*, in the zebra finch, and in rodents, brain endocannabinoids seem to act as orexigenic mediators. In addition, AM251 induces suppression of rat food intake and food-reinforced behavior. Thus, our findings together with the above-mentioned observations and the known role of olfaction in food detection support the view that the ECS may play an important role in the response of organisms to their nutritional status, which has to be clarified in future studies.

THE EFFECT OF CANNABIDIOL ON MAST CELL FUNCTION IN ISOLATED GUINEA-PIG BRONCHI

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The plant-derived psycho-inactive cannabinoid, cannabidiol (CBD) has been reported to have immunosuppressive and anti-inflammatory properties in a range of animal models of immunomodulation and inflammation. In contrast, it was demonstrated recently that CBD has *pro*-inflammatory potential associated with mast cell activation and this effect was not mediated by the known cannabinoid receptors (*Giudice et al., J. Leu. Biol. 2007; 81:1-11*). Our objective was to further investigate the effect of CBD on mast cell degranulation induced by immunological and non-immunological stimuli in the guinea-pig bronchial preparation (GPBP). **Methods:** Heston guinea pigs of either sex (700-900 g) were sensitized and challenged with ovalbumin (OVA). 21 days later main bronchial rings (4-5 mm) were dissected and mounted in organ baths containing Krebs solution with indomethacin (10 μ M) for recording of isometric contraction to exogenously applied drugs. In addition, non-allergic responses were examined using the mast cell secretagogue, compound 48/80. Values are expressed as g contractions \pm s.e.m. Data were evaluated using Student's paired two-tailed *t* test.

Results: 1) Cumulative challenge with OVA (1-100 μ g/ml) induced concentration-dependent contractions in sensitized GPBPs. CBD at concentrations of 100 nM and 1 μ M, significantly inhibited the bronchoconstriction evoked by OVA 100 μ g/ml [CBD 100 nM: 0.34 g \pm 0.05 (n=6) vs. paired controls: 0.42 g \pm 0.03 (n=6), CBD 1 μ M: 0.06 g \pm 0.04 (n=6) vs. paired controls: 0.41 g \pm 0.07 (n=6)]. In contrast, CBD at 10 μ M produced significant potentiation of the immune response [0.60 g \pm 0.11 (n=6) vs. paired controls: 0.28 g \pm 0.02 (n=6)]. The histamine H₁ antagonist, mepyramine (100 nM) significantly attenuated the OVA effect [0.22 g \pm 0.04 (n=5) vs. paired controls: 0.42 g \pm 0.04 (n=5)]. The 5-lipoxygenase inhibitor, MK-886 (10 μ M) also produced significant inhibition [0.22 g \pm 0.03 (n=5) vs. paired controls: 0.37 g \pm 0.05 (n=5)] in sensitized GPBPs. 2) Cumulative challenge with compound 48/80 (1-300 μ g/ml) elicited concentration-related contractions in the GPBP. Pre-treatment with CBD (1 μ M) evoked significant reduction [0.22 g \pm 0.06 (n=4) vs. paired controls: 0.33 g \pm 0.06 (n=4)], while CBD (10 μ M) treatment resulted in a slight though non-significant enhancement of the contraction to compound 48/80 at the concentration of 300 μ g/ml [0.31 g \pm 0.05 (n=4) vs. paired controls: 0.20 g \pm 0.03 (n=4)]. Mepyramine (100 nM) significantly ($p < 0.05$) shifted the dose-response curve for compound 48/80 to the right, but the non-selective 5-HT_{1/2} receptor antagonist, methysergide (1 μ M) had no effect.

Conclusions: These results show that CBD modulates the mast cell-mediated contractile response in the GPBP in two ways. Low concentrations are inhibiting the response to OVA and compound 48/80 while higher concentrations are potentiating the response. The mediator released in response to both agents is histamine. In addition, 5-lipoxygenase products are mediators in the antigen-induced contraction of the GPBP. The observed effects of CBD may have implications for the development of cannabinoid-based treatments of asthma.

SYMPTOMS RELIEF AND IMPROVED MENTAL HEALTH IN FIBROMYALGIA PATIENTS USING CANNABIS. RESULTS OF AN OBSERVATIONAL STUDY

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Introduction: Fibromyalgia (FM) is a chronic disease that comprises diffuse pain and associated symptoms such as sleep disturbances, fatigue, stiffness, numbness, and cognitive disturbances. Moreover, it is frequently associated with chronic fatigue syndrome, irritable bowel syndrome, depression and anxiety. Since its pathophysiology remains unclear, pharmacological treatment is empiric and symptomatic, therefore only modest results are obtained. Some patients with FM use cannabis by themselves to relieve these symptoms. Self-reported evidence suggests that cannabinoids could help alleviate these symptoms. The aim was to describe cannabis patterns of use and the associated benefits referred by patients using cannabis in comparison to non cannabis users.

Methods: An observational, transversal and analytical study was performed. FM patients were recruited from 15 FM associations, one cannabis users association and one Rheumatology Unit, all located in Barcelona (Spain). A questionnaire was designed to collect data on patients' demographics, clinical data and characteristic of cannabis use (cannabis group). Cannabis users were further asked to record the perceived benefits of cannabis on a range of symptoms (pain, stiffness, relaxation, drowsiness, well-being) using 100 mm visual analogue scales (VAS) before and 2 hours after cannabis use. Both groups were asked to complete three questionnaires: Fibromyalgia Impact Questionnaire (FIQ), Pittsburgh Sleep Quality Index (PSQI) and the Short Form 36 Health Survey (SF-36).

Results: A total of 28 cannabis users and 28 non cannabis users patients were included. Both groups were similar in terms of age, gender, duration of FM, associated symptoms, concomitant disease and use of medication. In the cannabis group, 9 patients reported between 1 and 3 years of cannabis use, 8 reported more than 3 years of use, 8 reported less than 6 months and, 3 indicated duration of cannabis use between 6 month and 1 year. All of them used marihuana and the methods of administration were smoking (54%) and oral (46%). Most patients reported daily cannabis use (43%), 18% reported 2-4 times per week, 11% less than twice per week and, 29% reported only occasional use. Cannabis use was reported to reduce usual medication taken by 19(68%) subjects. VAS analysis indicated significant mean reduction for pain (37.1%: 95%-CI 26-48.1) and stiffness (40.7%: 95%-CI 29.1-52.3) and significant enhance of relaxation (27.6%: 95%-CI 7-48.2), drowsiness (20%: 95%-CI 1.1-38.8) and well-being (40%: 95% CI 27.3-52.6). In comparison to controls, the mental health component summary score of the SF-36 was significantly greater in the cannabis group ($P < 0.05$). No significant differences were found for the other questionnaires administered.

Conclusions: In our sample, cannabis use produces beneficial effects in some FM symptoms. Further studies of the utility of cannabinoids in FM as well as cannabinoid system involvement in their pathophysiology are warranted.

DRONABINOL IN CHRONIC PAIN - RESULTS OF A RETROSPECTIVE, CROSS-SECTIONAL SURVEY IN PATIENTS WITH NEUROPATHIC PAIN

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The role of the endocannabinoid system in the perception and processing of pain is confirmed and both spinal and supraspinal targets for cannabinoid-mediated analgesia have been identified. Case studies and first clinical studies on the use of cannabinoids have reported significant alleviation of pain or symptom control. The ReQuesD project (Retrospective Cross-Sectional Survey on Dronabinol) is the first attempt to collect systematically data on experience with treatment with dronabinol in chronic neuropathic pain.

Methods: Pain treatment centres with proven experience in providing treatment with dronabinol (i.e. ≥ 10 treated cases) and patients in treatment at these centres were identified. Patients were informed about the background and aims of the survey. After written consent the standardised, retrospective collection of the data from the physicians at the centres and protocol-based (differential) standardised telephone interviews were commenced.

Results: Data from a total of 124 patients (mean age: 54.5 ± 12.7 years) were collected in accordance with the protocol and included in the analysis. In 114 cases (93.4%) the onset of the illness was more than 3 years before the interview; 96 patients (84.2% (adj.)) were classified as fulfilling the criteria for Stage III of chronicity of the Mainz Staging System for evaluating the chronicity of pain. Mean pain intensity before treatment was 7.6 ± 1.7 (med 8) and was reduced to 4.2 ± 1.9 (med 4) during treatment with dronabinol. Corresponding changes were observed in the maximum intensity of pain (before vs. after): 9.1 ± 1.5 (med 10) vs. 5.7 ± 2.3 (med 6). Patients reported of a significant reduction in pain-related impairment: Before dronabinol 71.5% (adj.) showed strikingly high total mPDI (modified Pain Disability Index) scores, during dronabinol treatment only 21.1% (adj.). The health values obtained by SF-12 (Medical Outcomes Short-Form©) for the chronic pain patients improved significantly during treatment with dronabinol (physical health: improvement from 23.3 ± 6.8 to 33.5 ± 9.6 ; mental health improvement from 35.8 ± 9.1 to 47.5 ± 7.6). Retrospectively, the patients rated efficacy and tolerability of previous treatments with analgesics on a scale from 1 to 5 (1 = high, 5 = low) as 4.6 ± 1.2 (med 5) and 3.7 ± 1.5 (med 4). Their assessments of treatment with dronabinol were distinctly better: mean efficacy rating 2.1 ± 1.1 (med 2) and tolerability rating 1.6 ± 0.7 (med 2). In comparison to previous therapies the most frequent symptoms during therapy with dronabinol were increased appetite (26.6%), increase in weight (14.5%) and enhanced feeling of happiness (36.3%). The symptom of irritability more often disappeared (in 12.9% of patients).

Conclusions: In the present survey treatment of severely ill pain patients with dronabinol in advanced stages of chronicity proved to be highly effective and well tolerated. In addition to the clear, purely analgesic effect and its consequences for the degree of pain-related impairments of quality of life and independence, patients reported numerous other positive effects of dronabinol treatment on mood, depressiveness, affects, sleep patterns and coping and drive which are in line with current knowledge of the complex effects of the endogenous cannabinoid system on endogenous pain inhibition and/or control systems. These findings – especially in combination with its overall good tolerability profile - indicate that dronabinol is the concomitant medication of early second-choice treatment in patients with chronic pain in an advanced stage of chronicity.

PROTECTIVE EFFECT OF CANNABIDIOL IN RAT ISOLATED HEARTS SUBJECTED TO ISCHAEMIA-REPERFUSION

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Introduction: Cannabidiol, a major non-psychoactive constituent of marijuana, has potential therapeutic effects. So, there are recent evidences about its protective effect on cerebral ischaemia-reperfusion (IR) injury processes, although the definitive mechanism of this action is not clear. A cardiac IR process markedly affect the major cardiac parameters, either coronary flow or cardiac function. It has been described that while some cannabinoids (palmitoylethanolamide (PEA), 2-arachidonoylglycerol (2-AG)) can exert partial protective effects from cardiac IR (Lecipier et al., Br J Pharmacol 2003;139:805-815) others only limits the infarct size (anandamide, JW015, arachydonoyl-2-chloroethylamide, ACEA) (Underdown et al., Br J Pharmacol 2005; 146:809-816). The aim of the present study was to evaluate the effect of cannabidiol and O1918 on cardiac IR. Cannabidiol and O1918 have a pharmacological profiles different from those evaluated in cardiac IR untill now. They have been proposed as nonCB1/nonCB2 cannabinoid receptor antagonists.

Methods: Wistar rats isolated perfused hearts were mounted by the Langendorff technique and subjected to 45 minutes of global ischaemia following a reperfusion period of 60 minutes. The effect of the cannabidiol and O1918 (1 μ M each) (administered 45 minutes before IR) was evaluated. The cardiac parameters analyzed were: Coronary Perfussion Pressure (CPP), Left Ventricular Developed Pressure (LVDP), End Diastolic Pressure (EDP) and Heart Rate (HR).

Results: The IR process provoked a significant alteration of the cardiac parameters studied at the end of the experiment. Cannabidiol 1 μ M prevented the alterations induced by IR in all the parameters studied, resulting values similar to the control group at the end of the experiment. However, O1918 1 μ M did not completely correct the altered cardiac parameters obtained after IR, resulting some values similar to those obtained in the IR group.

Group	Δ CPP (mmHg)	Δ LVDP (mmHg)	Δ EDP (mmHg)	Δ HR (beats/minute)
Control	+21.71 \pm 12.26	-37.28 \pm 7.17	+17.51 \pm 4.12	+12.67 \pm 10.99
IR	+70.51 \pm 9.44**	-76.76 \pm 8.78**	+45.59 \pm 8.21*	-206.87 \pm 14.07***
CBD + IR	+23.81 \pm 10.67	-18.87 \pm 8.95	+20.96 \pm 7.79	-4.2 \pm 20.86
O1918 + IR	+68.05 \pm 9.21*	-51.17 \pm 12.38	+58.09 \pm 24.14**	-101.56 \pm 74.87*

Data represent the mean \pm ESM (n=5-7). For statistical analysis a two way ANOVA test was used (*P<0.05; **P<0.01; ***P<0.001 vs control).

Conclusion: These results suggest a potential therapeutic role of cannabidiol in cardiac ischaemia-reperfusion injury. Its protective effect does not seem mediated by a cannabinoid receptor mechanism. The definitive cannabidiol mechanism of action to protect on cardiac IR injury remains to be elucidated.

INDOOR AND OUTDOOR CULTIVATION OF CANNABIS: IS THERE AN EFFECT ON THE CHEMICAL COMPOSITION OF THE VOLATILE OIL

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The chemical composition of the volatile oil of cannabis as well as other constituents has been the subject of several investigations. Some of these investigations were directed toward establishing a chemical profile for plant materials of different genetic make up or different geographic origin. In forensic investigations, the question of where a specific seizure of marijuana was produced is commonly asked. We have previously described a procedure for determining the geographical origin of marijuana samples based on complete chemical profile of the samples' extracts using GC/MS. Broad classification was easily achievable, e.g. domestic vs. foreign, indoor vs. outdoor, and defining the country of origin of foreign samples was possible with high degree of accuracy (>80%). The method, however, was lengthy and labor intensive.

In an attempt to simplify the chemical profiling method and in recognition of the increased potency of illicit marijuana samples we embarked on a procedure that focuses on the chemical composition of the volatile oil. This avoids the high levels of cannabinoids and simplifies the chemical analysis.

This investigation is focused on establishing a protocol for the preparation of the volatile oil from different samples with consistency and establishing the best chromatographic conditions for the separation of the volatile oil constituents for GC/FID analysis. The protocol was used for the analysis of the volatile oil of marijuana samples of the same genetic make-up but produced by either indoor or outdoor cultivation.

Data will be presented showing sufficient differences to distinguish indoor vs. outdoor produced materials even if the plants were of the same genetic make-up (all produced from cuttings from the same mother plant).

This suggests that perhaps a procedure based on the analysis of the volatile oil of cannabis could be developed for establishing geographical origin.

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COMPASSIONATE USE OF SATIVEX – CLINICAL EXPERIENCE

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Over the last 7 years the new generation of Cannabis Based Medicines (CBM) have undergone clinical studies primarily focusing on MS related spasticity and neuropathic pain. Sativex (a CBM containing 27mg/ml delta-9-tetrahydrocannabinol and 25mg/ml cannabidiol formulated into an oromucosal spray) was granted regulatory approval in Canada in April 2005, but has yet to be licensed in the UK. In November 2005 the UK Home Office announced that Sativex could be prescribed as an unlicensed drug on a named patient basis for “Compassionate Use”. This allowed patients who were unable to participate in clinical trials to try the medicine. It also allowed the ongoing prescribing of Sativex for those who had participated in clinical trials but had no subsequent access to the drug in extension studies.

This poster will present the response to treatment with Sativex prescribed on a compassionate basis to a selection of patients with a variety of medical conditions who have found existing medications ineffective. There will be a breakdown on the medical conditions along with their symptoms for which Sativex has been prescribed. The Brief Pain Inventory (short form) was used to assess patients’ response to treatment and these results will be presented graphically in addition to selected individual case reports.

Summaries will be provided on patterns of dosing regimes, use of concomitant medication, and affects on sleep.

USE OF SATIVEX – PRESCRIBING ISSUES

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Over the last 7 years the new generation of Cannabis Based Medicines (CBM) have undergone clinical studies primarily focusing on MS related spasticity and neuropathic pain. Sativex (a CBM containing 27mg/ml delta-9-tetrahydrocannabinol and 25mg/ml cannabidiol formulated into an oromucosal spray) was granted regulatory approval in Canada in April 2005, but has yet to be licensed in the UK. In November 2005 the UK Home Office announced that Sativex could be prescribed as an unlicensed drug on a named patient basis for “Compassionate Use”. This allowed patients who were unable to participate in clinical trials to try the medicine. It also allowed the ongoing prescribing of Sativex for those who had participated in clinical trials but had no subsequent access to the drug in extension studies.

At the James Paget Hospital we have often been contacted by other doctors for information on prescribing Sativex. We have been involved in clinical trials with Sativex for 7 years and have continued the prescribing of the medication for patients after completing the trials. More recently we have become involved with prescribing Sativex for compassionate use, outside of clinical trials. This poster is to outline issues on prescribing and patient management that we have evolved, to inform other doctors who might wish to prescribe Sativex on a Compassionate Use basis.

Information on the aspects listed below will be presented on the poster;

1. Information on Sativex

A Physician Product Information Sheet and Patient Information Leaflet are available from Bayer along with information on obtaining the drug. However, the company are unable to disseminate this and other information about the use of the drug.

2. Funding

Given that Sativex has yet to obtain a licence from the MHRA, PCTs etc. are very unlikely to agree funding for individual patients. Therefore the patient may have to fund it themselves.

3. Presentation to the Patient

Initial Assessments

Assessment of pain and other symptoms and problems including - Brief Pain Inventory, concurrent medication, previous cannabis use, previous dependency and psychiatric problems, other contra-indications.

Instruction in Use

Taste of medication, possibility of irritation at application site, sites of use, schedule for titration and maximum limits, drug responsibilities & storage information, possibility of reducing other medications.

Side Effect issues

Drowsiness, dizziness, euphoria, psychosis, panic attacks, addiction, driving, use of alcohol

Miscellaneous Information

Patient is Home Office registered, illegality of other forms of cannabis, sole user of the medication, teenagers at home, travel out of the country, consent form, contact number for advice, liaison with GP, program of initial individual trial use of Sativex, subsequent management etc.

CANNABINOID RECEPTOR 2 (CB2) AGONIST, JWH INHIBITS GROWTH AND METASTASIS OF NON SMALL CELL LUNG CANCER

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Lung cancers are the most lethal cancers responsible for 26-31 % cancer deaths worldwide and grim (9-15%) 5-year survival rates. Non small cell lung cancers (NSCLC) form the bulk of lung cancer cases. High expression and activation of epidermal growth factor receptor (EGFR) in NSCLCs correlates with the aggressiveness and resistance of lung cancers to chemotherapy. In the present investigation we studied how cannabinoids receptor 2 (CB2) agonist JWH modulate EGFR mediated growth and metastasis in NSCLC cells. We observed CB2 receptor expression in human lung cancer samples as well as NSCLC cell lines A549 and SW-1573 used in this study. We found that pretreatment of the cells with JWH inhibited the EGF-induced migration and invasion of these cells at lower doses (100-250 nm) and growth at higher doses (5-10 μ m). Further signaling studies show reduced EGFR phosphorylation in JWH pretreated cells which was abrogated with CB2 antagonist treatment prior to the agonist showing the direct involvement of CB2 receptor in JWH mediated effects. In vivo experiments with JWH -133 administrations given at a dose of 1mg/kg body wt. resulted in considerable inhibition of growth and metastasis of malignant tumors generated in immunodeficient mice by injecting lung cancer cells. A significant reduction (~70%) in tumor weight and volume were observed in JWH treated animals compared to the vehicle treated animals. Similarly a significant (~50%) reduction was observed in the number of macroscopic lesions on the lung surface in JWH treated animals. Moreover, the inhibitory effect of CB2 agonist was absent in animals co-administered with CB2 antagonist SR14428. Immunohistochemical analysis of the tumor samples from different groups revealed anti-proliferative and anti-angiogenic effects of JWH, with significant reduction in staining for Ki67, a proliferative marker and CD31, an endothelial marker indicative of vascularization. Investigation into the growth inhibitory mechanism showed a cell cycle arrest in the G2 phase in NSCLC cell lines on JWH treatment. These results indicate that CB2 receptor agonist has anti-tumorigenic and anti-metastatic effects against lung cancer and may be targeted in developing novel therapies against lung cancer.

CANNABINOID ESTER CONSTITUENTS FROM HIGH POTENCY *CANNABIS SATIVA* L.

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Twelve new cannabinoid esters, together with three known cannabinoid acids and Δ^9 -THC, were isolated from a high potency variety of *Cannabis sativa* L. The structures were determined by extensive spectral analysis to be: β -fenchyl- Δ^9 -tetrahydrocannabinolic acid A ester (**1**), *epi*-bornyl- Δ^9 -tetrahydrocannabinolic acid A ester (**2**), α -terpenyl- Δ^9 -tetrahydrocannabinolic acid A ester (**3**), 4-terpenyl- Δ^9 -tetrahydrocannabinolic acid A ester (**4**), α -cadinyl- Δ^9 -tetrahydrocannabinolic acid A ester (**5**), inseparable mixture of two sesquiterpenyl- Δ^9 -tetrahydrocannabinolic acid A esters (**6**), γ -eudesmyl- Δ^9 -tetrahydrocannabinolic acid A ester (**7**), γ -eudesmyl-cannabigerolic acid ester (**8**), 4-terpenyl-cannabinolic acid A ester (**9**), bornyl- Δ^9 -tetrahydrocannabinolic acid A ester (**10**), α -fenchyl- Δ^9 -tetrahydrocannabinolic acid A ester (**11**), α -cadinyl-cannabigerolic acid ester (**12**), Δ^9 -tetrahydrocannabinol (Δ^9 -THC), Δ^9 -tetrahydrocannabinolic acid A (Δ^9 -THCA), cannabinolic acid A (CBNA) and cannabigerolic acid (CBGA).

Results: CB-1 receptor assays indicated that these esters, as well as the parent Δ^9 -THC acid A, are not active compared to Δ^9 -THC.

Future studies: Continue isolation and characterization, as well as biological testing of other new Cannabis constituents and study their possible contribution to the overall effects of Cannabis.

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