International Association for Cannabis as Medicine

in cooperation with
Institute of Biology, Pharmacognosy/Metabolomics, Leiden University
Office of Medicinal Cannabis, Ministry of Health, Welfare and Sports

IACM 3rd Conference on Cannabinoids in Medicine

9-10 September 2005

Leiden University

2005 Conference on Cannabinoids in Medicine

Place
Institute of Biology, Pharmacognosy/Metabolomics
Leiden University, Einsteinweg 55, 2300 RA Leiden

Registration Fee
150 Euros for both days
Students pay a reduced fee of 75 Euros for both days
Members of the IACM pay a reduced fee of 100 Euros for both days

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Special thanks go to our gold sponsors who allow us to have a wonderful evening dinner on Friday and to create the IACM Award. Another special thank goes to Bedrocan that allows participants of the meeting to visit its cannabis nursery and covers the costs of the travel from Leiden to Veendam.

Friday, September 9

08:00 – 08:45	**Registration**
08:45 – 09:00	**Greetings**

09:00 – 10:30 First Session (Clinical Studies)

09:00 – 09:15	Philip Robson, Derick Wade, Petra Makela, Heather House, Cynthia Bateman	Cannabis-based medicinal extract (Sativex) produced significant improvements in a subjective measure of spasticity which were maintained on long term treatment with no evidence of tolerance
09:15 – 09:30	Donald I. Abrams, Cheryl A. Jay, Hector Vizoso, Starley B. Shade, Haatem Reda, Scott Press, Mary Ellen Kelly, Michael Rowbotham, and Karin Petersen	Smoked cannabis therapy for hiv-related painful peripheral neuropathy: results of a randomized, placebo-controlled clinical trial
09:30 – 09:45	F. Markus Leweke, Dagmar Koethe, Christoph W. Gerth, Brit M. Nolden, Daniela Schreiber, Anita Hänsel, Miriam A. Neatby, Antje Juelicher, Martin Hellmich, Joachim Klosterkötter	Cannabidiol as an antipsychotic. a double-blind, controlled clinical trial on Cannabidiol vs. Amisulpride in acute schizophrenia.
09:45 – 10:00	Andrea Pelliccia, Gianpaolo Grassi, Angela Romano, Paolo Crocchiolo	Treatment with CBD in oily solution of drug-resistant paediatric epilepsies
10:00 – 10:15	Jeffrey Y. Hergenrather, Tod H. Mikuriya, David Bearman	Clinical improvement and reduction of immunosuppressive drug therapy in cannabis treated patients with Crohn's disease
10:15 – 10:30	Gernot Ernst, Claudia Denke, Marcus Reif, Martin Schnelle, Hartmut Hagmeister	Standardized cannabis extract in the treatment of postherpetic neuralgia – a randomized, double-blind, placebo-controlled cross-over study
10:30 – 11:00	**Break**	

11:00 – 12:30 Second session (Political and Social Issues)

11:00 – 11:15	Marco van de Velde	Two years of experience with legal production and distribution of medicinal cannabis in the Netherlands

11:15 – 11:30	Annemarie Janse, Nancy Breekveldt-Postma, Joelle Erkens, Ron Herings	Medicinal cannabis in the Netherlands
11:30 – 11:45	Louise Déry	Canadian Medical Marijuana Research Program: main purpose and accomplishments
11:45 – 12:00	Dolors Capellà, Marta Duran, Sergio Abanades	The therapeutic use of cannabis project in Catalonia: information, prescription and research
12:00 – 12:15	Dale Gieringer	The growth of cannabis medicine in the U.S.: practice & usage in a semi-legal regime
12:15 – 12:30	Mark Gibson	Canna-Biz Chocolate, production, and despatch to sufferers of multiple sclerosis
12:30 – 14:00	**Lunch**	

14:00 – 15:00 IACM General Meeting

15:00 – 15:45	**Review**	
	David Baker	Potential use of cannabinoids in multiple and amyotrophic lateral sclerosis
15:45 – 16:15	**Break**	

16:15 – 17:45 Third session (Basic Research)

16:15 – 16:30	Ester Fride, Tatiana Bregman, Oded Edelheit, Israel Hanukoglu, and Amiram Raz	Cannabinoids and cystic fibrosis (CF): different regulation of the endocannabinoid CB receptor system in CF mice
16:30 – 16:45	Natalya M. Kogan, Manuel Guzman, Ester Priel, Michael Schlesinger, Gergana Marincheva, Ronen Beeri and Raphael Mechoulam	Quinone type cannabinoids as anticancer compounds
16:45 – 17:00	Krisztina Monory, Federico Massa, Heike Blaudzun, Giovanni Marsicano, Beat Lutz	The role of different neuronal populations in the pharmacological actions of delta-9-tetrahydrocannabinol
17:00 – 17:15	Dagmar Koethe, Christoph W. Gerth, Daniela Schreiber, Brit M. Nolden, Sonja Gross, Antje Juelicher, Joachim Klosterkötter, Andrea Giuffrida, Daniele Piomelli, F. Markus Leweke	The endocannabinoid anandamide in CSF is related to the patterns of cannabis use in first-episode schizophrenia

17:15 – 17:30	Philipp-Alexander Brand, Andrea Paris, Jens Scholz, Kristina Lueken, Peter Tonner	Cannabinoids and their interaction with anesthesia in mice
17:30 – 17:45	Roger G. Pertwee, Lesley A. Stevenson, Ruth A. Ross, Martin R. Price, Gemma L. Baillie, Kerrie N. Wease and Adèle Thomas	The plant cannabinoid, delta-9-tetrahydrocannabivarin, selectively antagonizes R-(+)-WIN55212, anandamide and delta-9-tetrahydrocannabinol

18:00 Bus to Kurhaus Scheveningen

IACM Award Ceremony

During the evening dinner in the Kurhaus Scheveningen 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 Solvay Pharmaceuticals, GW Pharmaceuticals, Biocanna and Bayer plc for making this evening dinner and the IACM Award possible.

Evening Dinner

Dinner will be served in the Kurhaus, Jan Toorop Room, Gevers Deynootplein 30, Scheveningen (phone: +31 70 416 26 36) at 19.00. The evening dinner and one drink is included in the registration fee.

Transportation to the Kurhaus: Busses ('Brouwers' Tours') will leave from the conference centre at 18.00. Arrival at the Kurhaus between 18.30 and 19.00. Please come to the busses immediately after the end of the lectures.

On arrival in Scheveningen you can choose to have a stroll along the beach or on the boulevard, or have a drink in the bar near the Jan Toorop-room (own cost). If you choose to have a stroll, it is a good moment to buy presents, if you wish so.

Transportation to Leiden after the dinner: Busses will leave shortly after dinner. Please make sure to be in time for your bus. Departure time will be announced at the end of the dinner. Busses will stop at: Van der Valk Hotel Leiden, Holiday Inn Leiden and Hotel Het Witte Huis, and then end up at Leiden Central Station, where cabs are available usually for going to other hotels. (For a stop at Den Haag Cntral Station ask the driver on leaving the Kurhaus.)

For those who want to stay in Scheveningen and return later: (1) Take a city tram (line 9) or a bus (line 22) to the Central Station. This takes approximately 30 to 45 minutes. A ticket can be bought in the tram or bus. (2) Buy a ticket to Leiden in the Central Station Hall (2nd class, one way costs € 2,90). Trains are leaving 4 times per hour at 10, 29, 40 and 59 minutes after the hour, until 0.29. It takes 13 to 19 minutes to go to Leiden (depending on the hour). In Leiden you can take a cab to the hotel.

Public transportation in the Netherlands is safe, even after dark. Nevertheless we advise to take a seat in the front part of city trams. Especially in the station hall there can be pickpockets and people interested in the code of your bank pass.

Saturday, September 10

08:30 – 09:00 **Registration**

09:00 – 10:30 First session (Application and Pharmacokinetics)

09:00 – 09:15	L. Zuurman, C. Roy, A. Hazekamp, R. Schoemaker, J. den Hartigh, J.C.M.E. Bender, R. Verpoorte, J.L. Pinquier, A.F. Cohen, J.M.A. van Gerven	Effect of THC administration in humans: methodology study for further pharmacodynamic studies with cannabinoid agonist or antagonist
09:15 – 09:30	Tjeert Mensinga, Irma de Vries, Maaike Kruidenier, Wim Scholten, and Jan Meulenbelt	Pharmacokinetics and effects of cannabis at higher exposure levels
09:30 – 09:45	Arno Hazekamp, Renee Ruhaak, Lineke Zuurman, Joop van Gerven, Rob Verpoorte	Optimized administration of THC for clinical use by vaporizing
09:45 – 10:00	Donald I. Abrams, Hector P. Vizoso, Starley B. Shade, Cheryl Jay, Mary Ellen Kelly and Neal Benowitz	Vaporization as a smokeless cannabis delivery system: a pilot study
10:00 – 10:15	Thomas Nadulski, Fritz Pragst, Gordon Weinberg, Patrik Roser, Martin Schnelle, Eva-Maria Fronk and Andreas Michael Stadelmann	Randomized, double-blind, placebo-controlled study about the effects of cannabidiol (CBD) on the pharmacokinetics of delta-9-tetrahydrocannabinol (THC) after oral application of THC vs. standardized cannabis extract
10:15 – 10:30	Floris de Jong, Frederike Engels, Jaap Verweij, and Ron Mathijssen	Influence of medicinal cannabis on the pharmacokinetics of the anti-cancer agents docetaxel and irinotecan

10:30 – 11:00 **Break**

11:00 – 12:30 Second session (Miscellaneous)

11:00 – 11:15	Richard E. Musty and Jose Andre de Sousa Crippa	Potential therapeutic effects of cannabinoids on anxiety, a review

11:15 – 11:30	Marieke van Haaster	Facts and phantasy, cannabis and MS
11:30 – 11:45	Yosef Sarne, Bella Tselnicker, Chagi Pick and Ora Keren	Dissociating between the neuroprotective and neurotoxic effects of THC (delta-9 tetrahydrocannabinol)
11:45 – 12:00	Anita Holdcroft, Caroline Doré, and Susan Tebbs	Qualitative measures of mood and sensory responses to cannabis extract (Cannador) in THE CANPOP Study
12:00 – 12:15	Christian Giroud, Frank Sporkert, Arno Hazekamp, Marc Augsburger, Florianne Monnet-Tschudi, Patrice Mangin	Chromatographic-mass spectrometry procedures for determination of cannabinoids in blood and brain tissues. Application to forensic cases and pharmacological studies
12:15 – 12:30	Jörg Fachner	Comparing topographic EEG brainmapping changes of cannabis induced and sound-trance induced altered state of consciousness
12:30 – 14:00	**Lunch**	

14:00 – 15:00 Poster session

15:00 – 15:45	**Review**	
	Vincenzo Di Marzo	The role of endocannabinoids in gastrointestinal inflammation
15:45 – 16:15	**Break**	

16:15 – 17:45 Third session (Side effects, risks and problems)

16:15 – 16:30	John Zajicek	Lessons learnt from the CAMS study
16:30 – 16:45	Aaron B. Ilan, Alan Gevins, Kemi Role, Hector Vizoso, Donald I. Abrams	The cognitive neurophysiological effects of medicinal marijuana in HIV+ patients with peripheral neuropathy
16:45 – 17:00	Sergio Abanades	Cannabis and neuropsychological performance: results form a 3 year follow-up study
17:00 – 17:15	F. Grotenhermen, G. Leson, G. Berghaus, O. Drummer, H.P. Krüger, M. Longo, H. Moskowitz, B. Perrine, J. Ramaekers, A. Smiley, R. Tunbridge	Developing per se laws for driving under the influence of cannabis (DUIC)
17:15 – 17:30	Emmanuel S. Onaivi	An endocannabinoid hypothesis of substance abuse

17:30 – 17:45	Ethan B. Russo	Sativex adverse event profile and comparison with Marinol and “medical grade cannabis” in clinical studies

17:45 End of the Meeting

Posters

Poster Session on Saturday, 14:00 – 15:00

Marta Duran, Eva Montané, Xavi Vidal, Joan-Ramon Laporte, Dolors Capellà	Cannabinoids as antispastic agents for multiple sclerosis: a qualitative systematic review
Arno Hazekamp, Rob Verpoorte	Solubilizing THC in water by cyclodextrins
Jonathon Arnold, Michelle Holland, Nathan Gunasekaran and John Allen	Cannabinoids exert potent anti-proliferative effects on human breast cancer cells
M.I. Martin, E. Burgos, C. Goicoechea, D. Pascual	WIN 55,212-2 versus ketamine in a peripheral neuropathy induced by paclitaxel
Patrick Meybohm, Philipp-Alexander Brand, Felix Renhof; Jens Scholz, Peter H. Tonner	Interaction of the general anaesthetic propofol and selective agonists for cannabinoid-receptor type 1 and 2
Michelle Holland, John Allen, Mary Bebawy, Basil Roufogalis, Jonathon Arnold	Cannabinoid modulation of p-glycoprotein efflux activity and expression
Rudolf Brenneisen, Johannes Mathis, Thomas Loher, Corinne Roth and Matthias Gugger	Add-on delta-9-tetrahydrocannabinol (THC) is ineffective in drug-resistant restless legs syndrome (RLS)
Andrei Sibaev, Birol Yuece, Martin Storr	Cannabinoid-1 receptor functioning within the ascending peristaltic reflex: new electrophysiological tools to investigate the spatial neuronal projections
Kirsten R. Müller-Vahl, Udo Schneider, Peter Gielow, Ralph Buchert, Georg Berding	I-124-AM281 PET imaging of CB1-receptors in schizophrenia: a case study
Inmaculada Crespo, Raquel Gómez, Guillermo Moreno, Gustavo González-Cuevas, Jose Antonio López-Moreno And Miguel Navarro	Interaction between cannabinoid system and orexin A in feeding regulation

Luciano Angelucci, Mauro Bianchi, Claudio Cappuccino, Francesco Crestani, Salvatore Grasso, Lucia Palmisano and Massimiliano Verga on behalf of the Scientific Committee of ACT	Preliminary data from an ongoing survey on the therapeutic use of cannabis in Italy
Marta Duran, Segio Abanades, Rafael de la Torre, Magí Farré, Dolors Capellà	Pilot clinical trial protocol to evaluate preliminary efficacy and tolerability of a cannabis medicinal extract in patients with chemotherapy induced nausea and emesis
Mohamed Ben Amar	Therapeutic potential of cannabinoids
T.H. Mikuriya, W. North, F. Lucido, R. Jaffee, J. Weirick	Cerebrospinal delayed allergic reaction to pesticide residue
Floris de Jong, Desirée van Boven-van Zomeren, Arno Hazekamp, Robert Oostrum, Johan Bender, Erik Wiemer, and Jaap Verweij.	In vitro cytotoxicity of four cannabinoids (THC, THC-acid, CBD, and CBN) in a panel of six cancer cell lines
Zlatko Mehmedic, Jason Martin, Susan Foster and Mahmoud A. ElSohly	Delta-9-THC and other cannabinoids content of confiscated marijuana: potency trends,1993-2003
Tatiana Bregman, Yankel Gabet, Itai Bab, Oded Edelheit, Israel Hanukoglu, and Ester Fride	The endocannabinoid system and cystic fibrosis CFTR-/- mice: a look at osteoporosis and sex differences as revealed by cannabinoid administration
E. Gkoumassi, M. J. Dröge, B. G. J. Dekkers, C.R.S. Elzinga, H. Meurs, J. Zaagsma and S. A. Nelemans	Cannabinoid signaling in human bronchial epithelial cells
R. J. M. Niesink, S.M. Rigter, F.T.A. Pijlman, M.G. Bossong	Increase in total delta-THC in nederwiet as sold in Dutch coffee shops
Matthijs G. Bossong, Raymond J.M. Niesink.	How cannabis induces schizophrenia. An integrative hypothesis from the neurobiological literature.
Tom Schefter, Birgit Stürmer, Werner Sommer, Martin Schnelle, Andreas Stadelmann	Effects of cannabis and delta-9-tetrahydrocannabinol on response priming in humans
Hassan Rashidi, Wouter A. Duetz, Rob Verpoorte	Production of more soluble cannabinoids by bacterial biotransformation

Visit to Bedrocan BV

On Thursday, 8 September, and on Sunday, 10 September, there will be a possibility to visit the cannabis nursery of Bedrocan. The bus will depart at 12:00 on Thursday from the Van der Valk Hotel and be back at about 21:00. On Sunday the bus will depart at 9:00 and be back at about 18:00.

Oral Presentations

CANNABIS-BASED MEDICINAL EXTRACT (SATIVEX) PRODUCED SIGNIFICANT IMPROVEMENTS IN A SUBJECTIVE MEASURE OF SPASTICITY WHICH WERE MAINTAINED ON LONG-TERM TREATMENT WITH NO EVIDENCE OF TOLERANCE

Philip Robson[1], Derick Wade[2], Petra Makela[2], Heather House[1], Cynthia Bateman[1]

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[2]Oxford Centre for Enablement, Windmill Road, Oxford OX3 7LD, UK

Introduction: Patients with multiple sclerosis (MS) usually experience a range of impairments, of which muscle spasticity is often prominent and disabling. Following completion of a double-blind, placebo-controlled trial of a cannabis-based medicinal extract (CBME) in the symptomatic treatment of MS, patients were given the option to enter a long-term follow-up trial to determine whether benefits seen following CBME might be maintained over many months of treatment.

Methods: Acute study: a randomised, placebo-controlled, double-blind parallel group study over six weeks of treatment at three centres in the UK. Eligible patients were experiencing significant problems from at least one of the following: spasticity, spasms, bladder problems, tremor or pain. CBME (Sativex) containing equal amounts of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), and placebo was delivered by oro-mucosal spray in a self-titrated dose up to a maximum of 48 sprays (120mg of THC and CBD) daily in divided doses. Primary symptoms were measured by 100 mm visual analogue scale (VAS).

Long-term study: Patients completing the acute study were eligible for inclusion in this open label study. Participating patients attended the clinic at eight-weekly intervals, completed a weekly symptom and intoxication diary using VAS, and recorded daily CBME doses.

Results: 160 patients completed the acute study, with daily doses following self-titration averaging 15 sprays of CBME (37.5mg of THC and CBD) and 26 for placebo. In the 39 patients with spasticity as their primary symptom VAS spasticity scores fell by 31.2mm following CBME and by 8.4mm following placebo (95% CI for difference –35.52, -10.07; SE 6.26; $p = 0.001$). Diary scores produced a similar result ($p = 0.009$). 137 patients entered the long-term study and were followed for an average of 434 days (range 21-814), and 58 (42.3%) withdrew for the following reasons: lack of efficacy 24; adverse events 17; withdrawn consent 6; lost to follow-up 3; other 8. Sixty-six patients with spasticity completed 82 weeks CBME treatment. At entry to the acute study this group had a mean VAS spasticity score of 69.5, which had reduced to 34.2 on entry into the long-term study. After 82 weeks, the mean score was 31.8 and average daily dose had reduced marginally from 12 sprays on entry to 10 sprays at the last assessment. Similar reductions were seen in VAS measures of bladder-related problems, muscle spasm and pain in the long-term patients. Sudden interruption of CBME for two weeks in a sub-group of 25 patients did not result in a consistent withdrawal syndrome. Commonest unwanted effects were oral irritation from the ethanolic spray, dizziness, diarrhoea and nausea but these were generally mild to moderate in intensity and well tolerated.

Conclusion: Beneficial effects of CBME (Sativex) on spasticity (and other symptoms) in MS seem to be maintained over long-term treatment, with no evidence of tolerance.

SMOKED CANNABIS THERAPY FOR HIV-RELATED PAINFUL PERIPHERAL NEUROPATHY: RESULTS OF A RANDOMIZED, PLACEBO-CONTROLLED CLINICAL TRIAL

Donald I. Abrams, Cheryl A. Jay, Hector Vizoso, Starley B. Shade, Haatem Reda, Scott Press, Mary Ellen Kelly, Michael Rowbotham, and Karin Petersen

The University of California San Francisco, San Francisco, California 94110, USA

INTRODUCTION: There is significant evidence that cannabinoids may be involved in the modulation of pain, especially of neuropathic origin. HIV-related painful peripheral neuropathy is a significant medical problem with unsatisfactory treatment options. Based on the effects of cannabinoids in pre-clinical models of neuropathic pain and anecdotal case reports, a controlled trial of smoked cannabis was conducted.

METHODS: Following a 16 patient open-label pilot proof-of-concept phase that suggested a beneficial clinical effect of seven days of smoked cannabis, a follow-on randomized, placebo-controlled trial was conducted. Fifty participants with painful HIV-related neuropathy and baseline pain scores $\geq$ 3 on a 10 point visual analog scale were admitted to the General Clinical Research Center for a 7-day inpatient stay. Participants smoked one 3.56% tetrahydrocannabinol containing cigarette or a matching placebo three times daily for five days. In addition to the effect of smoked cannabis on the subjects' chronic clinical pain, the impact on an experimental heat/capsaicin pain model was also evaluated. The primary endpoints were the reduction and relative reduction in neuropathic pain as assessed by average daily pain scores as well as the effect of smoking on acute experiemntal pain. A $\geq$30% reduction in pain was considered to be significant for this analysis. Reduction in experimental pain was a secondary outcome measure.

RESULTS: Fifty of the 56 randomized participants (43 men, 7 women, mean age 48 years) completed the placebo-controlled trial; 25 on each arm. Patients had an average of 6 years of neuropathic pain. In 17 cases the neuropathy was felt to be secondary to HIV alone, in 26 secondary to HIV medications and to both in 7. Baseline characteristics were well-matched across study arms. Thirteen of the 25 patients who were randomized to marijuana cigarettes reported greater then 30% reduction in pain during the intervention phase, compared with 6 of the 25 patients receiving placebo cigarettes ($p=0.04$). The pain reduction was greater in the group receiving marijuana (34%) than in the group receiving placebo (16.7%). The marijuana group also experienced a similar significant reduction in response to the experimental pain model compared to placebo recipients. Adverse events were not appreciated in this trial.

CONCLUSION: Smoked marijuana is effective in reducing chronic ongoing neuropathic pain as well as acute pain in the experimental pain model. The magnitude of the response of the neuropathic pain is similar to what is seen with gabapentin, a widely used therapeutic intervention for HIV neuropathy.

Acknowledgements: The University of California Center for Medicinal Cannabis Research and NIH Grant 5-MO1-RR00083

CANNABIDIOL AS AN ANTIPSYCHOTIC. A DOUBLE-BLIND, CONTROLLED CLINICAL TRIAL ON CANNABIDIOL VS. AMISULPRIDE IN ACUTE SCHIZOPHRENIA.

F. Markus Leweke[1], Dagmar Koethe[1], Christoph W. Gerth[1], Brit M. Nolden[1], Daniela Schreiber[1], Anita Hänsel[1], Miriam A. Neatby[1], Antje Juelicher[1], Martin Hellmich[2], Joachim Klosterkötter[1]

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The endogenous cannabinoid system has recently been shown of particular importance in the pathophysiology of acute schizophrenia. It interacts with various neurotransmitter systems in the central nervous system including the dopaminergic, glutamatergic and GABAergic system. While the psychedelic properties of the natural cannabis compound delta-9-tetrahydrocannabinol are widely known, there is some experimental and clinical evidence that other herbal cannabinoid compounds may have antipsychotic properties.

Based on these confounders we designed a four week, double-blind, controlled clinical trial on the effects of purified cannabidiol, a major compound of herbal cannabis, in acute schizophrenia and schizophreniform psychosis compared to the antipsychotic amisulprid. The antipsychotic properties of both drugs were the primary target of the study. Furthermore, side-effects and anxiolytic capabilities of both treatment strategies were investigated.

Cannabidiol significantly reduced psychopathological symptoms of acute psychosis after both, week two and four, when compared to the initial status. There was no statistical difference of this effect to the control condition. In contrast, Cannabidiol revealed significantly less side effects when compared to Amisulpride.

This phase II clinical trial on the effects of Cannabidiol in acute schizophrenia and schizophreniform psychosis raises evidence for its antipsychotic properties that exceeds by far the evidence from open observations available up to now. Furthermore, it raises evidence that the endogenous cannabinoid system may provide a valid target in the search for new treatments for schizophrenia.

Acknowledgements: Funded by the Stanley Medical Research Institute (00-093 to FML) and the Koeln Fortune Program (107/2000 + 101/2001 to FML).

TREATMENT WITH CBD IN OILY SOLUTION OF DRUG-RESISTANT PAEDIATRIC EPILEPSIES

Andrea Pelliccia[1], Gianpaolo Grassi[2], Angela Romano[1], Paolo Crocchiolo[3]
on behalf of the Scientific Committee of ACT (Associazione Cannabis Terapeutica – Italy).

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[3] American University of Rome, 00100, Italy

Introduction: As shown by Turkanis et al. (Epilepsy, 1979), cannabidiol (CBD), similarly to δ9-tetrahydrocannabinol (δ9-THC) and *Phenytoin* (PHT) increases the "afterdischarge" and seizures threshold, mainly at the limbic level, without exhibiting the side effects induced by drugs such as PHT. Studies on rats were conducted that confirmed the *anticonvulsant* effects of both CBD (Chiu et al., 1979) and of δ 9-THC (Cosroe and Mechoulam, 1987). However, in spite of other studies having confirmed the anticonvulsant effect of cannabinoids, up to date no trials were conducted on man and, the less so, on the child.

Methods: We collected data on a population of children who presented with traditional antiepileptic drugs-resistant seizures, treated with a 2.5% corn oily solution of CBD as part of an open study, by modulating administration and titration schedules on a case by case basis, according to clinical response.

Results: On June 2002 we started to treat an eleven year-old girl affected with a highly drug-resistant Lennox-Gastaut syndrome, with CBD, a substance not included in the list of illicit drugs, in a 2.5% corn oily solution, administered at gradually increasing doses up to the present 20 drops daily. Results have been encouraging: the girl, since she assumes CBD, did not need any longer to be admitted to hospital for her epileptic seizures, while her attacks decreased both in frequency and intensity, in addition her awareness, postural tone and speaking ability improved, as to allow us to gradually decrease her barbiturate intake. Along the same line, CBD was proposed to another patient, a 17 year-old boy with an equally drug-resistant Lennox-Gastaut syndrome: although he reached the dose of only 30 drops daily, he also exhibited a slight improvement of the crises and, first and foremost, a clear-cut attention-behavioural improvement, and even in his case a suspension of the barbiturate treatment was initiated. During the last year, 16 more children were started on CBD, all of them affected with symptomatic drug-resistant epilepsy; however, only 9 out of these are currently on treatment, since the parents of the remaining children, although appreciating the improvement of their offspring, not only concerning the fits but also the awareness and the muscular tone, preferred to discontinue due to the economic overcharge induced by the treatment (approximately 300 Euros per month).

Conclusions: So far obtained results in our open study appear encouraging for various reasons: 1) no side effects of such a severity were observed as to require CBD discontinuation; 2) in most of the treated children an improvement of the crises was obtained equal to, or higher than, 25% in spite of the low CBD doses administered; 3) in all CBD- treated children a clear improvement of consciousness and spasticity (whenever present) was observed.

CLINICAL IMPROVEMENT AND REDUCTION OF IMMUNOSUPPRESSIVE DRUG THERAPY IN CANNABIS TREATED PATIENTS WITH CROHN'S DISEASE

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California physicians involved in the practice of cannabis consultations regularly encounter patients with autoimmune and idiopathic inflammatory conditions. Patients with Crohn's disease occupy a proportionate number of these cases. The Crohn's patients encountered by these physicians have been treated with a variety of conventional pharmacological therapies including steroids, other immunomodulators and a number of biologic therapies, including anti tumor necrosis factor. Some have already had severe anorectal complications such as obstruction, fistula and abscess formation resulting in surgical intervention. The authors interviewed and examined patients seeking a physician statement of recommendation as required by California law. The vast majority of these cases are non-naïve cannabis patients, i.e. they have found that the use of cannabis is associated with clinical improvement prior to seeking physician approval.

The primary aim of this pilot study is to evaluate the efficacy of the ad lib use of natural cannabis in alleviating the symptoms of active Crohn's disease both with and without concomitant use of steroids and other immunomodulators. A secondary aim of the study is to determine if cannabis in combination with steroids and other immunomodulators leads to better response, longer periods of disease quiescence, and reduction in the use of steroids and other immunomodulator pharmaceuticals.

We performed a retrospective chart review of 20 patients with Crohn's disease who were approved to use cannabis for relief of symptoms, including abdominal pain, diarrhea, fatigue, anorexia and weight loss as principal complaints. All patients studied had an independent diagnosis of Crohn's disease from their primary or specialist physicians. Inclusion criteria also included the completion of a follow-up questionnaire designed to elicit details of the clinical course and use of all medications including cannabis. Data were collected on patient demographics, clinical response to cannabis, prednisone dose, concomitant immunomodulator therapy, complications and adverse effects.

Preliminary results indicate that the majority of patients found a substantial improvement of their clinical course and a marked reduction or discontinuation of conventional pharmaceutical therapy following the regular use of cannabis. Co-therapies included azathioprine (AZA), 6-mercaptopurine (6-MP), methotrexate (MTX), Infliximab (anti-TNF alpha), prednisone, mesalamine, and antibiotics. Cannabis purportedly serves as an effective immunomodulator, antispasmodic and appetite stimulant with a wide margin of safety and freedom of undesirable adverse effects compared with conventional pharmacotherapy.

STANDARDIZED CANNABIS EXTRACT IN THE TREATMENT OF POSTHERPETIC NEURALGIA – A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CROSS-OVER STUDY

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Introduction: Patients with postherpetic neuralgia suffer frequently from spontaneous pain and allodynia and adequate treatment is still a challenge. Approaches with non-opioids, opioids, antidepressants and antiepileptics influence these bothersome symptoms often only to a minor or moderate extent. The aim of this study was to determine the maximal tolerable dose (MTD) of orally administered standardized cannabis extract (2.5 mg THC and 1.2 mg CBD per soft-gelatine capsule) in the treatment of postherpetic pain and allodynia.

Methods: 26 patients who suffered from postherpetic pain for at least 6 months and did not show satisfactory symptom relief during this time have been included into this trial. Basic treatment with analgesics, antidepressants or antiepileptics was maintained during the entire study. Exclusion criteria were neuralgic pain, psychiatric diseases, drug dependency, coronary heart disease and arrhythmias. Concomitant use of analgesics was permitted. After a two-week run-in phase without study medication to measure baseline condition, patients were randomized to arm A (verum first) or arm B (placebo first). Beginning with 2 capsules/d (cannabis extract equivalent to 5 mg THC, or placebo) the dosage was increased every four days up to 8 capsules (20 mg THC/d, or placebo) until symptoms disappeared or adverse effects developed. This optimal dose was maintained for four weeks. A two-week wash-out phase was followed by additional 4-weeks of active, or placebo treatment with an identical dose (sham) escalation pattern. For pain assessment, a validated pain diary (Heidelberger Pain Diary), the McGuill Pain Questionnaire, and daily Visual Analogue Scale (VAS-) Pain Scores were applied. Other secondary parameters were the amount of analgesics used as well as size of the hyperalgesia and allodynia region. To measure health-related quality of life, we used the Medical Outcomes Study (MOS) 36-Item Short Form (SF-36). Physical health was checked with neurological examination including quantitative sensory testing (QST). The study was reviewed and approved by the local ethics committee.

Results: 26 patients were randomized; 3 patients dropped out before commencing the second treatment phase after cross-over due to reasons not related with study medication. No major side effects were reported. Minor adverse events included dizziness, dry mouth, slight tachycardia, nausea and increased appetite. Statistical analysis is pending; main results will be presented at the meeting.

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TWO YEARS OF EXPERIENCE WITH LEGAL PRODUCTION AND DISTRIBUTION OF MEDICINAL CANNABIS IN THE NETHERLANDS

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After a lobby by patients and patient unions during many years, the Dutch government decided that medicinal cannabis should be available in pharmacies as a prescription medicine. An important argument for this was that some 10.000 patients used already medicinal cannabis illegally and that the quality of their medication was uncertain. By dispensing medicinal cannabis of pharmaceutical quality the health hazard for these patients is reduced.
The Office of Medicinal Cannabis (OMC) sells medicinal cannabis on behalf of the government to pharmacies from 1 September 2003 on. This went technically well. It was shown that medicinal cannabis can be cultivated in such a way that it complies to all pharmaceutical requirements, like constant composition and chemical and microbiological purity (absence of heavy metals, pesticides, fungi and bacteria). The Office produces two varieties and a third variety with a high cannabidiol content will soon be introduced.
The entire production process is performed under Good Agricultural Practices (GAP), Good Manufacturing Practices (GMP), Good Control Laboratory Practices (GcLP) and Good Distribution Practices (GDP). The Office audits its contractors and has a quality system. It aims to be certified by ISO 9002-2000 later this year. Methods for analytical control were worked out and applied on each batch.
Before the introduction of medicinal cannabis in the pharmacies, mainly the voices of the pros were heard. A survey early 2003 showed that a large majority of the GP's and other physicians were in favour of prescribing medicinal cannabis. However, after the sick fund council (CVZ) advised negative on reimbursement by the public health insurance, many physicians followed them in their critical and negative attitude, some of them even comparing cannabis with homeopathy publicly. An unexpected effect was that illegal distributors of cannabis took the opportunity to increase their market share. They spread persistent rumours about the official cannabis, exaggerating price differences and falsely pretending that prescription of medicinal cannabis was prohibited for certain indications. The papers adopted these rumours with ease. Unfortunately, this resulted in many patients continuing buying their medicinal cannabis at illegal outlets, like coffee shops and a 'patients foundation'. Things became worse, when one of OMC's own growers said on TV that his cannabis did not work.
Mainly because of these rumours, a majority of the patients still uses cannabis from illegal sources in 2005. This results in a loss on the OMC's sales and endangers the continuation of the legal production and distribution. The same people who once lobbied for legalisation of medicinal cannabis successfully, are now killing its production. The minister of Health announced in the mean time, that he will decide on the continuation later in 2005 and required that the program will earn back its own costs. With the end of distribution to pharmacies, also the affordable production for scientific purposes would come to an end.
The announcement in March 2005 by Hazenkamp that fungal contamination of illicit cannabis is a public health hazard may result in a turning point. The OMC seeks the support of patients associations (MS, cancer, aids) to spread this message that patients should use the safe cannabis of the OMC, but it will take some time to see the effects of these measures.

MEDICINAL CANNABIS IN THE NETHERLANDS

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Introduction: In the Netherlands cannabis is available for medicinal purpose in the pharmacies upon prescription by a medical doctor since September 2003. This research was done to study the characteristics of patients that start to use cannabis from the pharmacies.

Methods: A national enquiry was started to identify all patients who were prescribed medicinal cannabis. Patients were contacted by their pharmacist to fill out a questionnaire. The questionnaire contained items about characteristics of patients; complaints and morbidity; use of cannabis; experiences with other cannabis products. Furthermore, history of drug use was collected.

Results: In total 200 patients returned a questionnaire whereas drug history was available for 175 of these patients. 67% of the respondents were female, and 60% of all respondents had used cannabis before. The main indications for cannabis use were chronic pain (72.5%) and muscle cramp/stiffness (53.0%). Among the cannabis users, 42.0% suffered from multiple sclerosis and 11.0% were diagnosed with rheumatic diseases. The history of drug use showed a relatively frequent use of analgesics (36.6%) and psycholeptics (34.9%). Experiences with previous use of other cannabis products indicated that concomitant drug use could be decreased in 40.4% of the patients, remained the same in 48.6% and increased in 0.9%; in total 10.1% did not use any concomitant drugs. Most reported side effects of previous cannabis products were lethargy (42.5%) and dry mouth (38.1%).

Conclusions: The main indications for prescription of medicinal cannabis were chronic pain and muscle cramp/stiffness; multiple sclerosis was the most frequently reported disease. The majority of the patients had used other cannabis products before, resulting in a decrease in concomitant drug use in a substantial number of patients. Legalization did not cause an excessive increase of cannabis used, most likely to be explained by the more expensive drugs in the pharmacy compared to coffee shops.

CANADIAN MEDICAL MARIJUANA RESEARCH PROGRAM: MAIN PURPOSE AND ACCOMPLISHMENTS

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The Canadian research strategy on marihuana for medical purposes and related activities have been put in place as a compassionate approach and in response to public pressures and a series of court decisions in support of the use of marihuana for medical purposes. This situation has had a major impact on Health Canada's regulatory processes and operations. The department has put in place new regulations under the *Controlled Drugs and Substances Act (CDSA)* entitled the *Marihuana Medical Access Regulations (MMAR)* to authorize the use, possession and growing of marihuana for medical purposes. To apply these new regulations, Health Canada has had to implement new operational/regulatory activities to grant authorizations, support clinical research and provide a "legal" source of marihuana to researchers and authorized patients. Health Canada has put in place a production and distribution capability to provide a reliable supply of quality, standardized marihuana for research and, since July 2003, to distribute for therapeutic purposes to authorized patients who wish to use Health Canada's marihuana.

Notwithstanding the court decisions, marihuana is not approved as a therapeutic product in any country and there have been few clinical trials on the use of marihuana for medical purposes. In addition, the Canadian medical community has serious concerns about the lack of evidence-based research on which to base the medical use of marihuana. The medical profession is also concerned with the potential harmful effects of smoking marihuana.

To meet responsibilities pursuant to the *Controlled Drugs and Substances Act (CDSA)* and the *Food and Drugs Act (FDA)*, the Federal Health Minister requires information on the risks and benefits related to the use of marihuana for medical purposes. For these reasons, Health Canada in partnership with the Canadian Institutes of Health Research (CIHR) has implemented, in 1999, a clinical research program on the use of marihuana, in smoked and non-smoked forms, to determine the risks and benefits of its use for medical purposes. The ultimate objective of his program is to investigate clinical treatments in patients unresponsive to usual treatments. The scope of the reserach program include the following health conditions: multiple sclerosis, chronic and severe pain, AIDS/HIV patients who have severe pain, cachexia, anorexia, weight loss and/or severe nausea and epilepsy and glaucoma. It is envioned that through this program abetter understanding of the safety and efficacy of using marihuana to control these symptoms will be forthcoming. Progress to date as well as challenges encountered in implementing such a researh program will be discussed.

THE THERAPEUTIC USE OF CANNABIS PROJECT IN CATALONIA: INFORMATION, PRESCRIPTION AND RESEARCH

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In 2000 the five political parties in the Spanish Catalan Parliament signed a proposal to legalize the use of cannabis for therapeutic purposes. This was the result of a "Grup Àgata" initiative, a 300 member association of women with breast cancer. The bill was approved by the Catalan Parliament but was lately refused by the central Government. Instead of cannabis, nabilone was approved in Spain -under the administrative status of foreign medication- as an adjuvant antiemetic in oncology patients who did not respond to standard treatment (corticoids and serotonin antagonists). However, nabilone has been only slightly prescribed. In 2002 our Clinical Pharmacology service prepared a technical report about the medical uses of cannabis and cannabinoids which concluded that further research is needed to precisely define the place of cannabis in therapeutics. However, the results of two prospective surveys made in Catalonia shows another reality: some patient groups find in cannabis an alternative treatment for their condition and there is an urge of information for these patients and their doctors. The Catalan Government set up a working group to define a therapeutic cannabis project with three primary objectives: 1) to facilitate the access to cannabis for patients who are already using it despite the limited information about its therapeutic benefits, 2) to provide rigorous information to doctors and patients about the therapeutic uses of cannabis, and 3) to promote clinical investigation with cannabis extracts to confirm their role in therapeutics. The aim of this presentation is to describe the components of this pilot project.

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THE GROWTH OF CANNABIS MEDICINE IN THE U.S.: PRACTICE & USAGE IN A SEMI-LEGAL REGIME

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While the US Supreme Court has recently upheld federal laws prohibiting medical cannabis, a growing number of states have laws protecting medical cannabis users from prosecution for possession or cultivation, and physicians may legally recommend its use.

Although sale of cannabis remains technically illegal, in California there has arisen a gray-market supply system of over 100 patients' clubs, dispensaries, and clinics, which continue to be widely tolerated despite occasional raids by federal and local police.

In this climate, medical cannabis use has expanded rapidly and is now well in excess of 120,000 patients. In some areas, users account for up to 1% of the population; in others, only 1 in 10,000. The variation is correlated to the local availability of physicians' clinics and cannabis dispensaries.

Surveys of medical cannabis physicians, clinics and patient registries show that there are over 200 different ICD-9 indications for cannabis, mostly clustered around diseases involving chronic pain, neuralgia, spasticity, nausea, and psychiatric disorders including PTSD, depression, and ADD. Many physicians recommend cannabis as a harm reduction substitute for other drugs, such as prescription analgesics, opiates and alcohol. An increasing number of users are obtaining medical recommendations for such everyday complaints as back pain, insomnia, and anxiety/stress.

The popularity of medical cannabis has led to charges that the law is being abused to protect non-medical "recreational" use. Surveys show that the great majority of patients have prior, non-medical experience with cannabis. In interviews with 2,799 California patients, Dr. Thomas O'Connell has identified a population of physically healthy users who manifest mood disorders, including ADD/ADHD, depression, dysphoria, anxiety, etc, The great majority are younger males with a history of adolescent alcohol or drug use. Dr. O'Connell proposes that this population benefits from cannabis for emotional therapy and as a harm reduction substitute for other drugs. An alternative interpretation is that they are non-medical "recreational" users.

The line between medical and non-medical use is hard to draw. Unfortunately, due to federal restrictions, research on the use of medical cannabis has been thin. In view of its broad range of efficacy and high pharmacological safety, the case can be made that cannabis is evolving in the direction of an over-the-counter drug for general adult use.

POTENTIAL USE OF CANNABINOIDS IN MULTIPLE AND AMYOTROPHIC LATERAL SCLEROSIS

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Introduction: Both Multiple Sclerosis (MS) and Amyotrophic Lateral Sclerosis (ALS) are neurodegenerative diseases of the central nervous system (CNS), but MS has a strong autoimmune component in the disease pathogenesis. Cannabinoids have been considered for symptom-modifying treatments but experimental data suggests that there may be the potential to control the immune-response and neurodegenerative processes.

Methods: Clinical data from published (symptom control) trials will be reviewed and indications of cannabinoid treatment of pre clinical studies in experimental allergic encephalomyelitisis (EAE) models of MS and the Superoxide Dismutase ($SOD1^{G93A}$) transgenic mouse model of ALS, including crosses with mice that lack elements of the cannabinoid system will be discussed

Results: Cannabinoids exhibit tonic control of symptoms of MS and ALS, such as spasticity in experimental models of human disease. There is increasing support for these observations from clinical trials. However experimental data and an increased understanding of the cannabinoid system, indicate that there is a potential for cannabis and cannabinoid related agents to slow the neurodegenerative processes that drive disease progression and accumulation of chronic disability. This can be shown in both EAE and SOD1 models of neurodegeneration, which indicate that cannabinoids can regulate both (auto)immune-dependent and autoimmune independent elements of disease.

Conclusion: Cannabinoids can control signs of disease by CB_1 and non-CB_1-dependent mechanisms and importantly have the potential to slow disease progression. The inability to truly dissociate the therapeutic from adverse effects of cannabis may open the way for agents that target the endogenous cannabinoid system to control symptoms and the neurodegenerative processes that cause disability in both MS and ALS.

Acknowledgement: The research was supported by AIMS2CURE, Brain Research Trust, The Multiple sclerosis Society of Great Britain and Northern Ireland and The Wellcome Trust. We thank Ben Cravatt, Catherine Ledent and Beat Lutz for originally supplying cannabinoid mutant mice and the Cannabinoid Research Community for supplying agents and relevant expertise too numerous to mention.

CANNABINOIDS AND CYSTIC FIBROSIS (CF): DIFFERENT REGULATION OF THE ENDOCANNABINOID CB RECEPTOR SYSTEM IN CF MICE

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Introduction: Cystic fibrosis (CF) is the most prevalent lethal autosomal recessive disorder in the Caucasian population, affecting 1 in 2500 newborns. The disease is expressed as the formation of viscous secretions affecting several organs, mainly the lungs and the digestive system; osteoporosis occurs in about 30% of the patients. A defective chloride channel is considered as the primary etiological factor. However, impaired fatty acid balance as found in CF, may be responsible for inflammatory lung disease. Endocannabinoids, being derivatives of fatty acids, are affected by dietary levels of fatty acids (*Berger et al., PNAS, 2001*). We have hypothesized (*Fride, J. Cannabis Ther. 2002*) that cannabinoid treatment may relieve symptoms associated with CF.

Aims: a. to investigate the potential link between the CB_1 receptor system and unsaturated fatty acids; **b**. to investigate cannabinoid receptor sensitivity in CF compared to normal mice and **c.** to investigate the effects of chronic treatment with Δ^9-THC on developing cftr $^{-/-}$ mice, a transgenic mouse model for CF.

Methods: a. Lung tissue of CB_1 receptor knockout $CB_1^{-/-}$ mice, were analyzed for fatty acid concentrations (arachidonic acid, AA, docosahexaenoic acid, DHA). **b.** Behavioral and physiological response to the potent CB_1 receptor agonist HU210 (0.004 mg/kg) were assessed in adult $cftr^{-/-}$ and wild type mice. **c.** Δ^9-THC was injected (5mg/kg, between day 7-28 of age) daily to $cftr^{-/-}$, $cftr^{+/-}$ and $cftr^{+/+}$ mice. Survival and weight gain were assessed throughout development and at adulthood. Cannabinoid-related functions were assessed at adulthood.

Results: a. Decreased DHA/AA ratios were detected in the lungs of $cftr^{-/-}$ mice compared to their wild type and carier $cftr^{+/-}$ counterparts. **b.** Acute HU210 administration significantly decreased motor activity, but only in males. HU210 induced hypothermia in male and female $cftr^{-/-}$ mice but not in *wildtypes*. Intestinal motility was greatly inhibited by HU210 but less so in CF mice.

c. Chronic daily Δ^9-THC injections did not improve survival of $cftr^{-/-}$ mice. Weight gain was transiently increased in normal and carrier ($cftr^{+/-}$ mice), but not in $cftr^{-/-}$ mice. Motor activity was selectively reduced by Δ^9-THC in $cftr^{-/-}$ females. Intestinal motility was low in CF females but was not further affected by Δ^9-THC treatment.

Conclusions: 1. The DHA/AA fatty acid imbalance in the lungs of $CB_1^{-/-}$ receptor knockout mice resembles that reported in $cftr^{-/-}$ mice, thus supporting a link between the endocannabinoid CB receptor system and symptoms of CF. **2.** The current regimen of chronic treatment with Δ^9-THC did not improve survival of CF mice. **3.** The absence of cftr-selective effects on motor functions and pain perception, together with positive cftr-selective effects on temperature and intestinal regulation, is consistent with the peripherally restricted nature of CF symptoms. **3.** CF mice were resistant to the weight gain-enhancing effects of Δ^9-THC.

Overall, these results suggest that the endocannabinoid CB receptor system is abnormal in CF mice from the early developmental stages, warranting further investigation of the Endocannabinoid CB Receptor systems in Cystic fibrosis.

QUINONE TYPE CANNABINOIDS AS ANTICANCER COMPOUNDS

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INTRODUCTION: Anthracyclines, a large group of quinonoid compounds produced by different strains of streptomyces, exert antibiotic and antineoplasic effects. They are used to treat some forms of cancer. Though highly effective in cancer therapy, these compounds are not selective, acting on cancer and other cells by numerous mechanisms and thus also causing side effects, which limit their use. The development of quinonoid compounds that display antineoplastic and/or anti-angiogenic activity, but are more selective and less toxic is a major therapeutic goal.

METHODS: HU-331 (cannabidiol-hydroxyquinone) was synthesized from cannabidiol by KOH_{aq}. Its structure was determined by NMR and X-ray crystallography. The ability of HU-331 to kill numerous human cancer cell lines was assayed by MTT test. For *in-vivo* test HT-29 colon carcinoma was transplanted to *nude* mice. The tumors were stained for determining blood vessel development. For assaying the mechanisms of HU-331-mediated cancer cell death several standard methods were used. The ability of HU-331 to inhibit topoisomerases was assayed on puc19 plasmid relaxation. The enantiomer of HU-331 was synthesized and tested alongside HU-331 itself. For evaluation of the anti-angiogenic action of HU-331 and some other cannabinoids, collagen-embedded rat aortic rings were incubated for 5-7 days with these compounds in the presence of FGF or VEGF (or with FGF/VEGF alone as positive controls). The ability of cannabinoids to inhibit endothelial cell proliferation was assayed as well. The cardiotoxicity of HU-331 compared to doxorubicin was assayed on mice by echo-cardiography.

RESULTS: HU-331 shows very high effectivity against human cancer cell lines *in-vitro* and also against *in-vivo* tumor grafts in nude mice. At 35 days after cancer cell injection, the tumors in the treated group were half the size of the tumors in the controls. HU-331 is highly selective. It does not cause cell cycle arrest, cell apoptosis and caspase activation. HU-331-caused cell death is partially mediated by ROS. HU-331 does not act through binding to any receptor, but probably enters the cell and acts through its quinone moiety. HU-331 has limited influence on topoisomerase I action, but is able to inhibit topoisomerase II even in nanomolar concentrations. HU-331 is strongly anti-angiogenic. It partially inhibited aortic ring angiogenesis in concentrations as low as 0.1 μg/ml (300nM). The number of new vessels formed was not only lower, but even those that were formed were shorter. HU-331 also caused endothelial cells apoptosis. The tumors treated by HU-331 contaqined much less vessels than control tumors. In comparative assays HU-331 inhibited Jurkat (T cell lymphoma) cells growth more than some known anticancer drugs (doxorubicin, mitoxantrone and etoposide). In echo-cardiography tests HU-331 (7.5 mg/kg/week) is much less toxic than doxorubicin (1.5 mg/kg/week)

CONCLUSION: The cannabinoid quinone HU-331, which is more selective, more potent and less toxic than most known anticancer quinones and also possesses high anti-angiogenic activity, specifically inhibits topoisomerse II and thus has a high potential as a new anticancer drug.

THE ROLE OF DIFFERENT NEURONAL POPULATIONS IN THE PHARMACOLOGICAL ACTIONS OF Δ^9-TETRAHYDROCANNABINOL

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Δ^9-Tetrahydrocannabinol (THC) exerts profound effects on the brain through CB1 receptors. As CB1 is expressed in distinct neuronal populations in the central nervous system, we were interested in elucidating the exact roles of these neuronal populations in the well-known pharmacological actions of THC. We have generated a CB1 knockout mouse line and a number of CB1 conditional knockout mouse lines by the Cre / loxP system to dissect the involvement of different neuronal subpopulations in the physiological and pharmacological effects of agonists acting at the CB1 receptor. We have tested mice lacking CB1 expression in distinct neuronal populations in the so-called "tetrad" battery of pharmacological experiments. Here we present data showing that GABAergic forebrain interneurones are not required for the manifestation of the typical pharmacological / behavioural symptoms produced by THC treatment: hypolocomotion, hypothermia, catalepsy and increase of nociceptive threshold. Depolarisation induced suppression of inhibition (DSI) and LTD of inhibitory synapses (I-LTD) in the hippocampus were normally present in mice expressing CB1 only on GABAergic interneurones and were abolished in mice lacking CB1 expression from GABAergic neurones. This indicates that the physiological actions of endocannabinoids were conserved in mice irresponsive to THC. These results show that "classical" pharmacological actions of THC do not depend on functional expression of CB1 on GABAergic interneurones, paving the way for a novel interpretation of cannabinoid pharmacology.

THE ENDOCANNABINOID ANANDAMIDE IN CSF IS RELATED TO THE PATTERNS OF CANNABIS USE IN FIRST-EPISODE SCHIZOPHRENIA

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Background: Cannabis use has been considered a risk factor for relapse and an influencing factor on the pattern of psychotic symptoms in schizophrenic patients. The underlying neurobiological mechanisms for these long standing clinical observations remain conjectural. This study investigates the influence of previous and present cannabis use on the recently suggested adaptive role of the endocannabinoid system in first-episode, antipsychotic-naive schizophrenic or schizophreniform psychosis.

Methods: Concentrations of the centrally acting endocannabinoid anandamide were measured in cerebrospinal fluid (CSF) and serum of acute psychotic patients (n = 47) and of healthy volunteers (n = 81) by HPLC/MS. Psychopathology in patients, patterns of cannabis use, and urine drug screenings in both groups were assessed independently.

Results: Acute paranoid psychotic patients with less than 5 times of cannabis use lifetime and no acute use (n = 25) show significantly higher levels of anandamide in CSF than comparable healthy volunteers (n = 55; P = .000). They also differ significantly from those patients with a history of more than 20 times but no recent use of cannabis (n = 9; P = .001). Levels of anandamide in CSF were reversely correlated to psychotic symptoms depending on the history of cannabis use.

Conclusions: The pattern and history of cannabis use in acute, first-episode, antipsychotic-naive schizophrenia yields a selective and significant association to anandamide in CSF. This if of particular importance as anandamide is suggested to play an adaptive role in acute paranoid psychosis and may enhance our understanding of the underlying neurobiology.

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CANNABINOIDS AND THEIR INTERACTION WITH ANESTHESIA IN MICE

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Background and Goal of study: △9-tetrahydrocannabinol (THC) is a long known substance with a wide range of in vivo effects. Among these are analgesic effects and alterations of the state of alertness from euphoria to drowsiness. However, the effects of THC on the action of intravenous anaesthetics is not known.

Materials and Methods: Twenty male mice (type: SV 129) received propofol or THC i.p. or both. Sedation was monitored employing a rotating rod with a cut-off time at 60 s. Analgesic effects were determined by tail flick unit with a cut-off time after 10 s.

Results and Discussion: After injection of 50 µg/g propofol a rapid onset of sedation was seen with a mean of 52.4 s on the rota-rod one min. post injection. Maximum sedation was reached after 2.5 min with 27 s on the rota rod. Thereafter sedation constantly diminished until 15 min post injection when the mice stayed 60 s on the rota-rod. Propofol had no analgesic effect. THC (50 µg/g) showed first analgesic effects after 2.5 min with 4.4 s tail flick (baseline: 3.2 s). A maximum was achieved after 20 min with 6.7 s tail flick. After 45 min this analgesic effect diminished slowly. THC had no sedative effect. The combination of both substances propofol and THC showed a reduction in analgesic effects of THC and the sedative effect of propofol was reduced. After a stepwise increase of the dose of propofol to 100 µg/g sedation in combination with THC was equipotent to 50 µg/g propofol as a mono substrate. An onset of the combination was registered after 1 min with 48.9 s, a maximum after 2.5 min with 27.9 s and an offset after 12.5 min.

Conclusions: THC is an effective analgesic drug in mice. When combined with propofol THC reduces sedation. The exact mechanism is not yet studied, but a possible depression of GABA mediated receptors through THC is known from studies related to memory.[1)]

Reference:

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THE PLANT CANNABINOID, DELTA-9-TETRAHYDROCANNABIVARIN, SELECTIVELY ANTAGONIZES *R*-(+)-WIN55212, ANANDAMIDE AND DELTA-9-TETRAHYDROCANNABINOL

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Introduction: This study focused on delta-9-tetrahydrocannabivarin (THCV), a little-investigated plant cannabinoid, that is an analogue of delta-9-tetrahydrocannabinol (THC) with a 3-propyl instead of a 3-pentyl side chain. We investigated whether THCV modulates contractions of the mouse vas deferens when administered alone or antagonizes cannabinoids or non-cannabinoids in this tissue. The ability of THCV to displace [^{3}H]CP55940 from CB_1 receptors or to activate or block CB_1 receptors in brain tissue was also determined.

Methods: Vasa deferentia obtained from adult MF1 mice were mounted in organ baths and contractions were evoked electrically or with β,γ-methylene-ATP or phenylephrine. THCV (GW Pharmaceuticals) was investigated by itself or added 30 min before *R*-(+)-WIN55212 (WIN), anandamide (AEA), THC, clonidine, capsaicin, β,γ-methylene-ATP or phenylephrine. Binding experiments were performed with mouse whole brain membranes. Drugs were dissolved in DMSO or saline.

Results: At concentrations in the range 10 to 1000 nM, THCV opposed the ability of WIN, AEA and THC to inhibit electrically-evoked contractions of the vas deferens, producing parallel dextral shifts in the log concentration response curves of these three cannabinoids (n=6 to 9). The mean K_B values of THCV against WIN, AEA and THC were 1.5, 1.4 and 36 nM respectively, indicating THCV to be more potent against WIN and AEA in this bioassay than against THC. THCV (100 nM) did not oppose the ability of clonidine or capsaicin to inhibit electrically-evoked contractions of the vas deferens. Nor did 3 to 1000 nM THCV inhibit electrically-evoked contractions when administered by itself. At 1 μM, neither THCV nor WIN altered the size of contractions induced by β,γ-methylene-ATP or phenylephrine, suggesting that THCV interacts with WIN at prejunctional sites in the vas deferens. In experiments with brain membranes, THCV displaced [^{3}H]CP55940 with a mean K_i value of 75 nM (n=4 to 8) and, at 1 μM, produced a parallel dextral shift in the log concentration-response curve of WIN for stimulation of [^{35}S]GTPγS binding (K_B = 85 nM; n=5). By itself, 1 μM THCV neither stimulated nor inhibited [^{35}S]GTPγS binding.

Conclusions: The data obtained from the brain membrane experiments suggest that THCV is a CB_1 receptor antagonist. However, THCV was more potent in antagonizing WIN and AEA in the vas deferens than in antagonizing WIN in brain membranes or in displacing [^{3}H]CP55940 from CB_1 receptors. Also, THCV was more potent in the vas deferens as an antagonist of WIN and AEA than of THC. Consequently, further experiments are required to establish the mode of action of THCV in this tissue.

EFFECT OF THC ADMINISTRATION IN HUMANS: METHODOLOGY STUDY FOR FURTHER PHARMACODYNAMIC STUDIES WITH CANNABINOID AGONIST OR ANTAGONIST

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Introduction: Cannabinoid receptor 1 agonists and antagonists are in development for neurological, metabolic and psychiatric disorders. The effects of cannabinoid antagonists in healthy volunteers are mostly unknown, hampering the design and interpretation of early pharmacology studies in humans with these compounds. Cannabinoid antagonist activity can be demonstrated, by showing inhibitory activity on the effects of the cannabinoid receptor 1 agonist tertrahydrocannabinol (THC). This study addresses the dose-response-relationships for THC. This information can be used as the basis for pharmacological proof-of-mechanism studies of cannabinoid antagonists (counteraction studies) and agonists (as a positive control). The study was also set up to identify by which pharmacodynamic parameters the effects of THC are most accurately quantified.

Methods: THC was purified from *Cannabis sativa* according to GMP-compliant procedures (Farmalyse BV, Zaandam, The Netherlands). Twelve healthy males (average 23.3 years, range 21-27) with a history of mild cannabis use for at least one year were included in the study. On one study day, rising doses of THC (2, 4, 6 and 8 mg) were administered by inhalation at 90-minute intervals using a Volcano® vaporizer (Storz-Bickel GmbH, Tuttlingen, Germany). On a separate, randomised occasion, vehicle was administered in the same way, as a double-blinded placebo. Pharmacodynamic measurements were obtained frequently after each consecutive dose, including: visual analogue scales (VAS) according to Bond&Lader, psychotomimetic VAS according to Bowdle, Saccadic Eye Movements, Smooth Pursuit Eye Movements, Pupil size, Body Sway, Adaptive Tracking, Pharmaco-EEG and Heart Rate. Bloodsamples were taken to measure plasma THC concentrations.

Results: Analysis was performed using mixed model ANOVA with baseline values as covariate. After THC administration, significant dose-related changes compared to placebo were seen in Body Sway (58.9%: 95% CI 33, 89.7) and VAS alertness (-33.6 %: 95% CI -41.6, -25.7). Significant dose-related changes were also seen in pharmaco-EEG, in which Pz-Oz delta- and beta activity decreased (-12.0%: 95% CI -19.1%, -4.4% and -8.0%: 95% CI -13.8%, -1.8% resp.). Heart rate increased significantly compared to placebo with a maximum of 24 beats per minute (19.4%: 95% CI 13.3, 25.5). Plasma THC concentrations showed little inter-individual variation. The average initial plasma half life was 4 minutes and the terminal half life was 70 minutes.

Conclusion: This study provides a model for pharmacological proof-of-mechanism studies of cannabinoid antagonists (inhibitory activity) and agonists (positive control).

PHARMACOKINETICS AND EFFECTS OF CANNABIS AT HIGHER EXPOSURE LEVELS

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Among the general population of Europe, cannabis is the most used illicit drug. Its main psychoactive constituent is Δ^9-tetrahydrocannabinol (THC). In recent years, concerns regarding cannabis use have been renewed because of the steady increase of THC content in netherweed in the past five years (on average, from 8.6% in 2000 to 20.3% in 2004). Part of the user scene, especially youngsters, do not adapt their consumption and smoke the entire joint, even when they know that the joint is highly potent. Their health may therefore be at stake.

Methods: a double blind, randomized, 4-way cross-over study with 24 regular male users (smoking 2-9 times per month) will be performed in spring 2005, with the object to evaluate the pharmacokinetics and effects of cannabis use. The four exposures are: a placebo (obtained from the National Institute on Drug Abuse, USA) and three relatively high THC content levels of respectively 33.0, 51.3 and 69.6 mg (obtained from the Office of Medicinal Cannabis, the Netherlands). Each joint will contain a mixture of 300 mg cannabis and 700 mg tobacco. Study parameters will consist of: serum THC (and metabolite) concentrations over time, heart rate, blood pressure, self-reporting questionnaires (e.g., a mood rating scale), and a collection of psychomotor tests. The psychomotor tests include: sustained attention tests (simple reaction time and a continuous attention test), a selective attention test (Erikson-Flanker Task), a short-term memory test (Sternberg), a motor response test (unstable tracking), and a dual task (unstable tracking plus short term memory test). During an additional selective attention task, event related potentials will be registered.

Results and conclusions: we hypothesize that an increase of the external dose will induce a dose-dependent increase in the internal exposure. Furthermore, an increase of the internal dose may in turn be responsible for an increase in the occurrence of cardiovascular effects (such as tachycardia and hypotension) and central nervous system effects (such as impairment of sustained attention and short term memory). This might considerably influence the behavior and performance of the exposed persons.

OPTIMIZED ADMINISTRATION OF THC FOR CLINICAL USE BY VAPORIZING

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What is currently needed for optimal use of medicinal cannabinoids is a feasible, non-smoked, rapid-onset delivery system. Smoking of cannabis plant material results in the highest bioavailability and consequently pulmonal administration of cannabinoids is considered to be very effective. The goal of this study was to evaluate the performance of the Volcano® vaporizer in terms of reproducible administration of pure THC, without the formation of degradation products. Results were used for designing a clinical trial for administration of THC by vaporizing.

Methods: Using the Volcano® cannabis vaporizer, THC and its acidic analogue THCA were tested for delivery of THC into the balloon of the Volcano device. The efficiency of vaporizing of these samples was compared with cannabis plant material. Analyses were performed using HPLC and quantitative ^{1}H-NMR. After determination of the dynamics of heating up, and accuracy and stability of vaporizing temperatures of the Volcano, the temperature setting and balloon volume were systematically optimized for maximum evaporation of THC. Factors contributing to loss of THC were evaluated. Several Volcano set-ups were tested to determine variability. After validation, the Volcano was used in a methodology study to determine the effects of pulmonary administration of a rising dose of THC in twelve healthy volunteers, who were subjected to an array of physiological and psychological tests after each administration.

Results: Under optimized conditions the Volcano was found to deliver about 54% of the loaded sample in a reproducible way into the vapor phase without formation of degradation products like delta-8-THC or CBN. In the range of 2 to 8 mg of THC the delivery was found to be linear with the amount of THC loaded onto the vaporizer. Prolonged storage of the balloon before inhalation resulted in an increasing loss of THC by condensation. No significant differences in THC delivery were found between four devices tested. Full results of this phase I clinical trial are not presented here, but a clear dose-dependent effect was found in several of the used tests. During these inhalation studies the fraction of exhaled THC was found to be around 34%. Improvements in the original design of the Volcano were made based on these results for further optimization of the Volcano for administration of pure cannabinoids in a clinical setting.

Conclusions: Using the Volcano for pulmonal administration of THC, a delivery is reached that is comparable to smoking, without the presence of degradation products or harmful byproducts in significant amounts. This study confirms that the pulmonary administration of cannabinoids by evaporation certainly has a clinical potential. With the Volcano a safe and effective cannabinoid delivery system seems to be available to patients. Although our current study has concentrated on the delivery of THC it should be noted that other cannabinoids might also have a role to play for some indications.

VAPORIZATION AS A SMOKELESS CANNABIS DELIVERY SYSTEM: A PILOT STUDY

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INTRODUCTION: The Institute of Medicine report published in 1999 suggested that although marijuana may have potential therapeutic value, smoking was not a desirable delivery system for cannabis. A 6-day "proof of concept" pilot study was proposed to investigate vaporization using the Volcano device as an alternative means of delivery of inhaled *Cannabis sativa,* to characterize preliminary pharmacokinetic and pharmacodynamic effects and to determine whether it may be an appropriate system for use in clinical effectiveness studies.

METHODS: Eighteen healthy subjects were recruited and admitted to the inpatient ward of the General Clinical Research Center (GCRC) at San Francisco General Hospital to investigate the delivery of cannabinoids by vaporization of marijuana compared to marijuana smoked in a standard cigarette. One dose (1.7, 3.4 or 6.8% tetrahydrocannabinol) and delivery system (smoked marijuana cigarette or vaporization system) was randomly assigned for each of the six study days. The primary endpoint was the comparison of plasma concentrations of delta-9-tetrahydrocannabinol (THC), cannabidiol, cannabinol, and metabolites, including 11-OH-THC resulting from inhalation of cannabis after vaporization vs smoking. Expired carbon monoxide was measured to evaluate whether the vaporizer reduces exposure to gaseous toxins as a secondary endpoint. We also evaluated physiologic and neuropsychologic effects and queried patients for their preference of blinded dose day and delivery method. Adverse events were collected.

RESULTS: 21 participants were enrolled to obtain the 18 who completed the 6-day inpatient study. 15 men and 3 women, mean age 30 years, were included in the final analysis. The plasma THC concentrations are still being determined at this time. Results will be available in September. 14 participants preferred vaporization, 2 smoking and 2 reported no preference. While still blinded with regard to dose, 8 participants selected the day they received 3.4% THC (7 vaporized, 1 smoked) as their most preferred treatment day; 4 selected the day they received 6.8% THC via vaporization and 6 had no treatment day preference. No adverse events were observed.

CONCLUSION: Vaporization of cannabis is a safe mode of delivery. The determination of plasma THC levels and comparison of clinical effects to smoked cannabis will provide information on the effectiveness of this delivery system. Participants had a clear preference for vaporization over smoking as a delivery system for the cannabis used in this trial.

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RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY ABOUT THE EFFECTS OF CANNABIDIOL (CBD) ON THE PHARMACOKINETICS OF DELTA-9-TETRAHYDROCANNABINOL (THC) AFTER ORAL APPLICATION OF THC VS. STANDARDIZED CANNABIS EXTRACT

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Introduction: Cannabidiol (CBD) was reported in the literature to modify the effects of delta-9-tetrahydrocannabinol (THC) by decreasing anxiety and antagonizing other THC-effects. The mechanisms of these effects of CBD are not yet clear although pharmacodynamic as well as pharmacokinetic mechanisms have been described. This study aimed to compare pharmacokinetic parameters of isolated THC and of a whole-plant cannabis extract and to investigate the effects of CBD on the pharmacokinetics of THC.
Methods: This was a double-blind, placebo-controlled, cross-over study in which each of 24 volunteers (12 males and 12 females, age 18-45 years) ingested soft-gelatin capsules with 10 mg THC (THC-set), cannabis extract containing 10 mg THC + 5.4 mg CBD (CAN-set) or placebo in weekly intervals. In an additional open-label part of the study 12 of the volunteers ingested the same dose of cannabis extract 1 h before a standardized breakfast (drug food interaction = DFI set). Blood samples were taken 30 min before and 30 min, 1 h, 2 h, 3 h, 4 h, 6 h, 9 h and 24 h after intake. The concentrations of THC, of its metabolites 11-OH-THC, THC-COOH and of CBD in the plasma samples were determined by automatic solid phase extraction, derivatization with N,O-bis(trimethylsilyl)triflouroacetamide and gas chromatography-mass spectrometry.
Results: The concentration vs. time curves (maximum concentrations C_{max}, corresponding time t_{max} and areas under the curves AUC) were evaluated by statistical methods with respect to equivalence or differences between the CAN-set and the THC-set caused by CBD and between the DFI-set and the CAN-set caused by the food ingestion. Furthermore, the intra-individual ratios of C_{max} and AUC for 11-OH-THC/THC, THC-COOH/THC and THC-COOH/ 11-OH-THC were compared between the THC-set and the CAN-set. Despite the large variation of the data, evidence emerged from the total of the results that CBD partially inhibits the cytochrome P450 catalysed hydroxylation of THC to 11-OH-THC under the conditions of this study. Furthermore, significantly higher AUC and C_{max} and shorter t_{max} were found for females as compared to males. No significant differences between the DFI-set and the CAN-set with respect to an effect of the food on the rate and yield of absorption or to a change of the first-pass metabolism were found.
Discussion: Inhibition of THC hydroxylation by CBD is particularly pronounced for oral intake since THC and CBD attain relatively high concentrations in the liver because of the high first-pass metabolism of THC. However, the effect of CBD observed in this study is small in comparison to the variability caused by other factors. The significant differences in the PK parameters between female and male volunteers are suprising as this was demonstrated so far only in animal models. The finding that no drug-food interaction has been observed in this study could be a consequence of the time of 1 hour between capsules administration and the standardized meal being too long.

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INFLUENCE OF MEDICINAL CANNABIS ON THE PHARMACOKINETICS OF THE ANTI-CANCER AGENTS DOCETAXEL AND IRINOTECAN

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Background: Back in 2003, in the Netherlands the production and distribution of a standardized cannabis-product for medical treatment purposes was legalized. Up to that moment, (cancer) patients, who thought they would benefit from it, were forced to obtain a non-standardized and possibly microorganism-contaminated cannabis-variant from their local 'coffee shop' for instance. Although there is still no role up front for medicinal cannabis in the treatment of pain, anorexia, and nausea in cancer patients, its use is frequently seen. Due to the broad spectrum of cannabinoids present in cannabis, undesirable pharmacokinetic drug-drug interactions with concomitantly prescribed anti-cancer drugs resulting in ineffective treatment or very severe side-effects (even sudden death) could not be excluded. Since cytochrome P-450 3A (CYP3A) isozymes are involved in the metabolism of most regular prescribed drugs, we have set up a study to investigate the effects of medicinal cannabis on the pharmacokinetics of two frequently prescribed anti-cancer drugs metabolized by CYP3A, namely docetaxel (Taxotere®) and irinotecan (Campto®).

Methods: Patients who full-filled all inclusion criteria (among others: a solid tumor for which no treatment option was available, adequate hematological, hepatic, and renal functions, no history of depression or other serious psychological or psychiatric condition) were treated with one course of docetaxel (180 mg iv) or irinotecan (600 mg iv) followed 3 weeks later by a second course, with concomitant medicinal cannabis once daily (0.2g/200ml tea), starting 2 weeks prior to infusion. Use of co-medication known to induce or inhibit CYP3A was not allowed, as was use of herbals and dietary supplements. Serial plasma samples were obtained up to 500 hours after infusion for pharmacokinetic analysis of docetaxel or irinotecan and metabolites.

Results: At time of analysis, 7 patients in each treatment arm were evaluable for analysis. For docetaxel no changes in dose normalized disposition and elimination profiles were seen between courses without and with medicinal cannabis co-administration. Mean clearance (CL) in the absence and presence of medicinal cannabis were 44.1 *vs* 40.6 L/h, respectively (P=.38). For irinotecan mean clearance (28.0 *vs* 26.0 L/h) and mean exposure (AUC) to its active metabolite SN-38 (506 *vs* 529 ng*h/mL) were equal as well (P>.42). Patients tolerated medicinal cannabis given as tea very well, although one patient complained about dysphoric mood. Patients were advised to take medicinal cannabis before going to bed. Sleepiness and better quality of sleep was reported frequently, whereas differences in nausea and vomiting were not reported.

Discussion: These data suggest that concomitant use of medicinal cannabis by cancer patients does not lead to altered metabolism of docetaxel and irinotecan with clinically relevant consequences. As medicinal cannabis tea does not seem to affect the side-effect profile seen in these patients negatively and the metabolism of both anti-neoplastics metabolized by CYP3A does not seem to be altered, the combination of medicinal cannabis with these anti-cancer drugs that are predominantly metabolized by CYP3A, may be considered safe. Nonetheless, until more clinical evidence becomes available, we advise to combine medicinal cannabis with (anti-cancer) drugs with a narrow therapeutic index only when other drugs have proven not to be effective and only in a controlled research setting.

POTENTIAL THERAPEUTIC EFFECTS OF CANNABINOIDS ON ANXIETY, A REVIEW

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A brief review of the effects of cannabinoid agonists, antagonists and other cannabinoids in preclinical animal models of anxiety will be presented. These studies lead to the conclusion that CB_1 antagonists, are anxiolytic. Agonists, on the other hand seem to have biphasic effects. Low doses seem to be anxiolytic, while high doses anxiogenic. Studies of cannabidiol (CBD) and cannabichromene also strongly suggest that they have anxiolytic properties. In addition, data on fatty acid hydrolase (FAAH) inhibitors, seem to be anxiolytic.

Following this a review of human studies with smoked *Cannabis* and CBD will be presented. These data extend the conclusion from animal studies. It seems that low doses of smoked *Cannabis* have anxiolytic properties at low doses. CBD has anxiolytic properties as well. For CBD, data will be presented from brain scanning studies. Tracer uptake after, CBD adminstration, was increased relative to placebo in the left parahippocampal gyrus and the left fusiform gyrus compared with placebo. Tracer uptake decreased in the CBD relative to placebo in the left amygdala-hippocampal complex and uncus, the hypothalamus and left superior portion of the posterior cingulate gyrus.

The brain area which showed increased activity in relation to placebo was the left parahippocampal gyrus. Deactivation of this area of the brain has been associated with panic attacks induced by lactate, anxiety induced by combat related images and autobiographical memory scripts. It seems that anxiety is associated with reduced parahippocampal activity, consistent with the findings that CBD increases activity in this brain area. Because activity in the CBD after CBD decreased relative to placebo, these data fit well since there is a large amount of data linking amygdala activation in a large variety of anxiety states. Similarly, the hypothalamus involved in various anxiety states, particularly in imaging studies, which have shown increases in hypothalamic activity in anxiety induced in normal volunteers and panic patients. These data are consistent with the anxiolytic effect of CBD. In regard to the posterior cingulate gyrus, increased brain activity is associated when viewing anxiety-provoking videos and provoked obsessions in obsessive patients. OCD patients, untreated, have increased metabolism in the brain area, which decreases with treatment and symptom remission.

In sum it seems clear that cannabinoids can be anxiolytic. We suggest that further clinical research should be conducted to confirm and extend these findings.

FACTS AND PHANTASY, CANNABIS AND MS

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Introduction: Before introduction of government cannabis, three providers took care of the delivery of cannabis on medical prescription. The most professional provider, Maripharm, had intern and extern laboratories where the product was analysed for years. Nowadays all three former providers are prohibited to supply cannabis.
Methods: An attempt to contact all cannabis using MS-patients about their experiences failed because of practical reasons. The MS-patients of one former provider, the SPMM, were send a standardised questionnaire. The questionnaire was sent to 233 patients, of which 170 participated; this gives a response rate of 73 percent. In addition a background and literature study has been performed.
Results:
Background: Although social demand for medicinal cannabis was the main reason for the introduction of government cannabis, the situation of a lot of patients who had already used cannabis actually got worse by it. The available knowledge and experiences are not used to their maximum extend. Consequentially the governments produce is greater than the demand.
Literature study: In the Netherlands only two cannabis studies with patients have been carried out. Even though international literature is available, important Dutch reports and advices base their conclusions on few rct-trials. There is a discrepancy between available studies and literature used by policymakers. This discrepancy had adverse effects on the situation for patients.
Empirical survey:
Use: Empirical research showed that most patients use cannabis to smoke it with tobacco or make tea from it. There is a growing use of preparing cannabis as tea. Although the doctors involved were positive about the use of cannabis, most patients had to find out the best use in practice.
Effects: Effects were especially found in symptoms which concern muscles (spasms/ spasticity, trembling, balance, tickling, muscle weakness and numbness), in symptoms involving pain (headache, pain in general, pain attacks, muscle cramps), and urinary symptoms (troubles with urinating/stool, frequently urinating at night, incontinence). At the same time, cannabis appeared to reduce problems concerning tiredness (fast tired, lack of energy), sleeplessness and mood (anxiety, depression).
Side effects: Reported side effects of cannabis use are generally positive effects on the mood (relaxation, calmness, euphoric feeling, mood improvement, sharpened mind). Negative side effects are reported too (increase in appetite, dry mouth, dull feeling, balance problems, decrease in concentration, worsening of short term memory, dizziness and tiredness).
Difference in treatment: A significant difference in frequency of effects and side effects was shown between patients who smoked cannabis with tobacco and patients who took tea. Patients who used cannabis in the form of a tea experienced significant less effect on their symptoms, but also fewer side effects.
Quality of life: Enquiry into the quality of life showed that patients are relatively happy. The experienced impact of cannabis on the health and mood situation is large. Most of the costs of medical cannabis were incurred by the patients and not the insurance companies, even though cannabis caused a decrease in costs because of the decrease in the use of other medicines, such as laxatives, pain-killers, muscle relaxers, anti-depressives, benzodiazepines, interferon's, inflammation reducers and opiodes. A few other medicines, and sometimes alcohol in small amounts, were taken in combination with cannabis. Only few interactions were experienced.

DISSOCIATING BETWEEN THE NEUROPROTECTIVE AND NEUROTOXIC EFFECTS OF THC (DELTA-9 TETRAHYDROCANNABINOL)

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Acute application of cannabinoid drugs has been shown to protect laboratory animals from various brain insults, including physical trauma and ischemia. On the other hand, chronic administration of the same drugs has been reported to induce cognitive deficits and morphological changes in the brain of the same species of animals. In light of the increasing interest in cannabinoid drugs as therapeutic agents, it is extremely important to identify the neurotoxic/ neuroprotective profile of cannabinoids, and to be able to dissociate between their beneficial and deteriorating effects. Based on our previous in vitro studies on the concentration-dependent dual activity of cannabinoids on intracellular calcium, we recently hypothesized that high doses of cannabinoids are expected to protect from neurological insults, while low doses are expected to induce brain damage *(Sarne and Keren, Med. Hypoth. 2004;63:187-192).*

In the present study we tested this hypothesis. We first determined the doses of THC that exerted either the "conventional" inhibitory effects, or a "paradoxical" stimulatory activity, in a battery of acute tests. We found that regular, high doses of THC (1-10 mg/kg) suppressed nociception, reduced body temperature and decreased motor activity in adult ICR mice, as expected. On the other hand, much lower doses (0.001-0.003 mg/kg) potentiated nociception, elevated body temperature and increased motor activity of the mice. We then studied the long term effects of a single low dose of THC using two different cognitive tests: spatial learning (Morris water maze) and passive avoidance (two-cage foot-shock avoidance). The two paradigms demonstrated a significant impairment of cognitive functions of mice up to 4 weeks following a single injection of low dose of THC. The behavioral deficits were comparable to those induced by other mild insults, such as minimal traumatic brain injury and metrazol-induced epileptic seizure, which were carried out in parallel experiments.

The long term effects of higher doses of THC, as well as the behavioral consequences of repeated applications of the drug that expose the organism to low concentrations of THC in the brain for long periods of time (due to the pharmacokinetic profile of this lipophilic drug) will be presented and discussed.

QUALITATIVE MEASURES OF MOOD AND SENSORY RESPONSES TO CANNABIS EXTRACT (CANNADOR) IN THE CANPOP STUDY

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Introduction: The CANPOP study was designed primarily to compare the analgesic responses of a single dose of cannabis extract, as Cannador (IKF Berlin), in the context of post surgical pain. Secondary outcome measures relating to central nervous system effects were sought.
Methods: Patient were recruited to an open label, dose escalating clinical study of one dose of Cannador after patient controlled analgesia with morphine was stopped following surgery. Exclusion criteria included central nervous system disease and use of cannabis within 6 weeks of the study. The use of escape analgesia was recorded over 6 hours after study drug administration. Mood effects were measured hourly using a 0-100mm visual analogue scale (VAS; 0 = best I could feel to 100 = worst I could feel) and using an open question at 6 hours 'has the treatment affected your mood?' *(Br. J. Anaesth. 91 (2003) 462P).*
Results: A dose-related response in requests for rescue analgesia was observed. All 11/11 (100%) patients in the 5mg group required additional analgesia, compared with 15/30 (50%) in the 10mg group and 6/24 (25%) in the 15mg group. The results for mood and sensory effects are shown in the Table. 1/11 patients at the 5mg dose reported feeling 'relaxed'. In the 10mg group 8 patients reported feeling a negative mood effect expressed as 'unpleasant', 'mad', 'out of body', 'aggressive', 'busy in my mind'. Positive mood effects in this group were recorded as 'pleasant', 'relaxed', and 'good'. One person experienced both positive and negative mood effects. There were a number of sensory experiences, mainly in the group that voiced a negative mood; they were visual 'saw shapes flying', proprioceptive 'not coordinated, floating' and 'strange sensations', and auditory 'sounds were amplified', 'hearing' changes.
Similar responses were recorded in the 15mg group. Negative feelings were expressed as 'feeling ill', 'going to die', 'paranoid', 'acute panic', 'unhappy', 'would not use it again', 'not worth the side effects', 'frightening' and 'do not like the strange sensations'. Positive effects were recorded as 'good spirits', 'very happy, good dreams', 'feeling nice, relaxed and mellow' and 'felt very happy'. Altered sensations were reported as visual 'difficulty in focussing', 'disorientated', 'burning' sensations, 'knives coming through neck' and 'heavy and pressed down'.

Table: The number of patients reporting mood and sensory effects from Cannador

Mood and sensory effects	5mg (n = 11)	10mg (n = 30)	15mg (n = 24)
Change in mood VAS, median [IQ]	-11[-82,16]	41[0,89]	-8[-38,96]
Positive mood	1	3	6
Negative mood	0	8	6
Sensory changes	0	5	5
No reported mood effects	10	17	12
Classical: 'high', 'stoned', 'trip'	0	2	1

Conclusion: Mood effects were observed in doses adequate for analgesia. They ranged widely and did not reflect classical word descriptors for recreational drugs.

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CHROMATOGRAPHIC-MASS SPECTROMETRY PROCEDURES FOR DETERMINATION OF CANNABINOIDS IN BLOOD AND BRAIN TISSUES. APPLICATION TO FORENSIC CASES AND PHARMACOLOGICAL STUDIES

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Cannabis has become a dual-use crop with many legal and illicit applications. Dual pharmacological effects have been also reported with cannabinoids exerting either neurotoxic or neuroprotective effects. To shed light on the complex relationship between favourable and unwanted side-effects and concentrations of active compounds at target organs and tissues, accurate methods able to quantify tiny amounts of cannabinoids must be available. Moreover, the body distribution of cannabinoids must be known to carry out realistic pharmacological studies. For instance, it is known that some cannabinoids exert in-vitro anti-inflammatory effects which can be of great benefit to patients suffering of inflammatory bowel diseases. However, it is not known whether the active concentration range measured in-vitro matches with levels which can be found in intestinal walls after cannabis intake.

In medico-legal practice, blood and urine levels are the only parameters available to the expert for forensic interpretation. On the other hand, in pharmacology experiments, if the administration dose is generally indicated, data about cannabinoid levels in treated biological specimens remain largely unknown. Gas-chromatography with mass spectrometry operating in the electron-impact mode is routinely applied to the determination of free THC, 11-OH-THC and THCCOOH in blood specimens of forensic cases. This method provides an adequate limit of quantification (i.e. about 1 ng/ml) with a good specificity. Blood from several hundred of car drivers from Western Switzerland has been examined using this method for the presence of cannabinoids. THC concentrations ranged between 0.4 and 35 ng/ml whole blood. A better sensitivity can be achieved by using chemical ionisation or MS/MS detection. This first approach is often limited to clinical and pharmacological studies because chemical ionisation results in poor fragmentation of cannabinoid molecules with an insufficient number of diagnostic ions for unequivocal identification. GC-MS with negative chemical ionisation operating in the selected ion monitoring mode was used to determine cannabinoid time-profiles in a double-blind crossover study that was carried out to compare the effects of 20 mg dronabinol and of 2 hemp milk decoctions containing 16.5 or 45.7 mg free THC with matched placebo on the driving capability. Because blood levels provide at best an approximation of cannabinoid concentrations at target tissues, brain analysis was carried out in some autopsy cases. Concentrations were found to be higher than blood levels somehow explaining why cannabinoid levels only partly reflect cannabis effects. Another strategy for cannabinoid determination is based on the use of liquid-chromatography coupled to mass spectrometry. LC with single quadrupole MS offers middle sensitivity and tentative identification of cannabinoids in various biological specimens. For instance, a Sciex LC-MS with TurboIonSpray ionisation was used to measure cannabinoids in rat brain aggregates treated with increasing amounts of THC. This method was also used to assess bile concentrations of THCCOOH-glucuronide, a molecule which is not amenable to GC-MS analysis because of its poor volatility. Triple-quad-MS and Ion-trap-MS^n technologies generally give better sensitivity and specificity. A ThermoFinnigan LTQ Linear ion Trap method with APCI has been developed to measure THC levels in biological fluids and tissues. Altogether, these data show that more and more analytical tools are made available to determine cannabinoids concentrations. However, only a paucity of data about cannabinoid distibution in body fluids is now available making it difficult to choose relevant cannabinoid concentrations and doses for *in-vitro* pharmacological testing. Finally, the uncovering of the relationship between brain and blood levels could give additional clues to the forensic expert and pharmacologist to interpret blood concentrations of cannabinoids in order to assess cannabis effects on human behaviour and performances.

COMPARING TOPOGRAPHIC EEG BRAINMAPPING CHANGES OF CANNABIS INDUCED AND SOUND-TRANCE INDUCED ALTERED STATE OF CONSCIOUSNESS

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Cannabis (Delta9-THC) is known to induce altered states of consciousness (ASC). ASC are also known to be induced from music absorption in ritualised settings, hypnosis, meditation, etc. EEG studies have correlated changes of ASC and found induction specific signatures. In a previous study the author has shown cannabis-induced EEG changes of music perception and in a further study he elicited trance induced EEG changes of music perception in a ritualised setting compared to rest. Both studies were done with the same EEG Brainmapper. This study aims to compare the results of cannabis and trance induced music perception. What indicates the difference of cannabis induced from music induced trance?

Methods: The results of two previous studies with an EEG Brainmapper (*Fachner 2002, JOCT 2: 3-36* ; *Fachner and Rittner 2004, Brain Topography 16: 121*) will be compared visually and quantitatively. First study compared three pieces of music in baseline and THC-induced altered state. Second study compared rest with a trance induction on a body monochord in a ritualised setting. Hypnotisability was measured with a Pekala's (*1991, West Chester PA, MID-Atlantic Educational Institute*) PCI-test. EEG- Results were averaged and treated with a t-Test and inspected with a visual topographic schedule. (T-Test comparisons of both study averages have not been obtained yet but will be ready for the meeting.)

Results: Diminutions in Theta waves, specifically in temporal regions (where primary auditory centres are located), while subjects were listening to music, were found in both conditions.

But EEG power in the temporal regions is further dampened after consumption of Cannabis. The EEG signature of the substance was recognizable in general synchronisation of the EEG and Alpha wave increase that characteristically influenced individual reactions to the music in EEG. Comparing pre/post music EEGs, differences ($p<0.01$) were found in the right frontotemporal cortex on Theta and on Alpha in the left occipital cortex. While monochord playing of the male subject induced frontal desynchronisation with increase of β-II-%, the female EEG showed a synchronisation with changes ($p<0.001$) in visual and somato-sensoric regions. Her α-changes might indicate change of processing to a trophotropic trance state. Both showed increase of β-II-% indicating ergotrophic trance. This study appears to show that reaction to trance induction is rather specific to the individual test person and their hypnotiseability.

Conclusions: Results showed a marked EEG signature of a cannabis induced ASC during music perception, which depends on the individual phamaco dynamic. Cannabis seems to temporarily intensify the personal cerebral strategy of auditory perception indicated with alpha enhancement and different interaction of visual and auditory brain regions. The trance induction on a monochord appears to elicit different, personal trance reactions, depending on the level of hypnotisability of a person. Other results in the literature support the result that a high hypnotiseability seems to be correlated with EEG synchronisation. According to Fischer's cartography (*1971, Science 174; 897-904*) of ASC Cannabis seems to induce a more trophotropic ASC. (Results of the t-Test between both study averages have not been obtained yet but will be presented in the meeting.) Cannabis induces a specific ASC reaction as revealed in EEG studies. Trance induction methods and the trance profile depend on the setting context and on the hypnotiseability of participants. Further studies on cannabis induced ASC should measure the hypnotiseability of study participants.

INVOLVEMENT OF THE ENDOCANNABINOID SYSTEM IN INTESTINAL DISORDERS WITH AN INFLAMMATORY COMPONENT

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For millennia *Cannabis* preparations have been used in folklore medicine for the treatment of a wide variety of disorders, including those affecting the gastrointestinal tract. It is well known that THC, the mayor constituent of *Cannabis,* binds to and activates two membrane receptors called CB_1 and CB_2 receptors. In the gastrointestinal tract, the CB_1 receptor are mostly found in myenteric neurons, but there is evidence of its presence, as well as of the expression of CB_2 receptors, also in intestinal epithelial cells. The capability of THC and synthetic CB_1 receptor agonists to inhibit intestinal motility in rodents has been shown. Moreover marijuana has been found to reduce diarrhea in humans (Di Carlo and Izzo, 2003). It was not surprising to find that also the endocannabinoid anandamide (AEA) exerts similar actions in mice. Evidence has accumulated in recent years to show that endocannabinoids and their receptors play a role also in the control of gastric emptying and intestinal peristalsis (Pertwee, 2001 for review). These effects seem to be mediated by peripheral CB_1 receptors that inhibit excitatory transmitter release in the enteric nervous system. In vitro studies on intestinal preparations demonstrated that the CB_1 antagonist(inverse agonist, rimonabant, accelerates intestinal motility, thus suggesting that the endocannabinoid system may be involved in physiological gut functions. Accordingly, Izzo et al. (2003) demonstrated that anandamide, via CB_1 receptors, exerts an antidiarrheal action in mice treated with oral cholera toxin (CT) which induces secretory diarrhea. Additionally, VDM11, a selective anandamide re-uptake inhibitor, prevents CT-induced intraluminal fluid accumulation. Ligresti et al. (2003) also described a potential role of the endocannabinoids in colorectal cancer growth inhibition. The authors found that the endocannabinoids levels are increased in transformed colon mucosa possibly to block proliferation via both CB_1 and CB_2 receptors, and suggested that compounds (such as VDM-11 and the FAAH inhibitor arachidonoylserotonin) able to inhibit endocannabinoid inactivation may be useful as anticancer agents.

The potential role of the endocannabinoid system in gastrointestinal disorders may extend even beyond the control of intestinal motility, colon propulsion, secretory diarrhea and colorectal cancer. In fact, two different studies, carried out in mice, in which small intestine and colon inflammation were induced by oral croton oil administration or DBNS intrarectal administration respectively, show that the endogenous cannabinoid system is physiologically involved in the protection against gut inflammation, and underlined a key role for CB_1 receptors (Izzo et al., 2001; Massa et al., 2004). However, no data have been reported yet in humans showing that the endocannabinoid system is activated during intestinal inflammatory conditions, and no study in animals has addressed the possibility that “indirect” agonists of cannabinoid receptors, i.e. inhibitors of endocannabinoid inactivation, might produce beneficial actions against inflammation in these conditions. In addition to discuss our current knowledge of the general role of the endocannabinod system in the small and large intestine, I shall report the results of recent studies carried out in my laboratory in collaboration with other groups, aiming at establishing a correlation between endocannabinoid levels in human intestinal mucosa and various pathological conditions, i.e. ulcerative colitis, diverticular disease and celiac disease, all characterized by inflammatory hallmarks. I will also provide the first example of how inhibitors of endocannabinoid degradation can be used against inflammation, at least in animal models.

LESSONS LEARNT FROM THE CANNABINOIDS IN MULTIPLE SCLEROSIS (CAMS) STUDY.

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The CAMS study was the largest clinical trial of cannabinoids yet conducted, and set out to test the hypothesis that cannabinoids may be helpful in treating symptoms of MS. 667 patients were randomised to one of three treatment groups: cannabis extract (Cannador), Δ^9-THC (Marinol) or respective placebo. Patients with relatively stable MS and significant spasticity (as determined by the Ashworth score) were titrated up to a maximally tolerated oral target dose over 5 weeks and then maintained at that dose for 8 weeks. After coming off medication over a few days, patients were then given the option of continuing previous medication in a blinded fashion for up to 12 months.

Results from the main study failed to show any significant effects on the primary outcome measure of spasticity using the Ashworth score. However, there were effects on walking time for those people taking Δ^9-THC and on subjective patient-reported scores of spasticity, muscle spasms, pain and sleep quality for both active treatment arms. Over the 12-month follow-up period, these subjective improvements continued in both active treatment groups. There were further improvements in the Ashworth scores and some of the disability scores for those people taking Δ^9-THC. There were no major safety concerns and overall the medication was well tolerated.

Conducting blinded controlled trials using medication with potential psychoactive side effects has been difficult. The active treatment groups correctly guessed treatment allocation more frequently than placebo, which leads to problems in the interpretation of subjective data. High levels (up to 50%) of placebo response highlight the importance of maintaining a placebo arm with adequate randomisation. Despite these issues, the evaluating physiotherapists did remain blinded to treatment allocation, and the Ashworth scores, walking times and Rivermead Mobility Index values were obtained by these physiotherapists.

The paucity of adequate measurement instruments when designing CAMS has led us to develop better instruments and outcome measures over the last 5 years. We have now produced a new patient-orientated spasticity scale, which splits the concept of spasticity into symptoms, psychological effects, and effects on movement and mobility. We are close to completing a new scale for the evaluation of neuropathic pain, and are using new disability scales that measure the overall impact of MS. Further studies are now being undertaken to substantiate the findings from the CAMS study and to further test the hypothesis that cannabinoids may have a greater role in the longer term management of progression in MS.

THE COGNITIVE NEUROPHYSIOLOGICAL EFFECTS OF MEDICINAL MARIJUANA IN HIV+ PATIENTS WITH PERIPHERAL NEUROPATHY

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Introduction: Animal and human data suggest that cannabinoids hold promise in treating the neuropathic pain that often accompanies diseases such as cancer and AIDS. If cannabinoids are to be used therapeutically in this regard, it is important to understand their side-effects on cognitive brain function. Accordingly, we evaluated the cognitive neurophysiological effects of cannabis by measuring electroencephalographic (EEG) signals and event-related potentials (ERPs) during performance of immediate working memory (WM) and delayed episodic memory (EM) tasks in a study assessing the safety and efficacy of smoked marijuana in patients with HIV-related peripheral neuropathy.

Methods: Twenty-four experienced marijuana smokers with a diagnosis of HIV-related peripheral neuropathy participated in a randomized, double blind, placebo-controlled study. Patients resided in the inpatient General Clinical Research Center at San Francisco General Hospital for 7 days, and smoked a placebo or marijuana cigarette (3.56% THC) 3 times daily during the last 5 days. Cognitive neurophysiological testing was performed on Day 2, on which no drugs were administered, and on Days 4 and 6, before and after the afternoon cigarette was smoked.

Results: Subjective measures of intoxication increased after marijuana smoking relative to placebo, but alertness and anxiety were unchanged. Marijuana did not affect reaction times in any of the tasks. However, after smoking marijuana WM task response accuracy decreased and cortical activation (as indexed by 9-11 Hz EEG alpha power) increased. In the EM task, marijuana led to a response bias in which even previously unseen words were categorized as having been seen before. Marijuana reduced attentional allocation during the EM task, as indexed by reduced N400 and Slow Wave ERP amplitude.

Conclusion: The results suggest that marijuana smoked by patients with HIV-related peripheral neuropathy directly or indirectly affects neurophysiological processes regulating immediate working memory and delayed episodic verbal memory. Patients who smoke marijuana to relieve peripheral neuropathy may therefore experience difficulty sustaining focused attention and remembering recently learned information for a few hours after each dose. Further research is required to understand the mechanisms underlying theses effects.

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CANNABIS AND NEUROPSYCHOLOGICAL PERFORMANCE: RESULTS FROM A 3-YEAR FOLLOW-UP STUDY

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Rationale: Ecstasy use has been associated with long-term learning and memory impairment. Similar patterns of impairment have been also described for cannabis users. Since ecstasy users usually consume cannabis and other drugs simultaneously, cannabis use could be a confounding factor during neuropsychological performance evaluation.

Objective: The aim of the present study was to investigate the neuropsychological profile associated with cannabis use either alone, or in combination with MDMA (recreational polydrug users), and describe the cognitive changes related to drug consumption along a three-year period.

Method: Tests of attention, executive functions, memory and learning were administered to three groups of subjects: 37 current polydrug users with regular consumption of both MDMA and cannabis, 23 current cannabis users, and a control group of 34 non-drug users. Subjects were evaluated after a period of at least 24h of abstinence for any drug. Four evaluations were carried out during three years.

Results: Our findings demonstrate a number of cognitive subclinical deficits in chronic MDMA polydrug users relative to non-users and cannabis group, relating to information processing speed, visual working memory and word fluency in baseline testing. Cognitive impairment was still observed in ecstasy users after two years of maintained polydrug use, with information processing speed as the only variable impaired. All deficits were subclinical due that results keep within the standard norms. Despite this fact, performance in ecstasy group constantly remained at a lower level compared to cannabis and non-users. In cannabis and polydrug users groups, the higher the consumption of cannabis, the worse the obtained results.

Conclusion: Our results seem to support that MDMA or MDMA/cannabis interaction could be responsible for the subclinical deficits observed. The main contribution of cannabis to that impairment seems to be related to an early age of onset of use. Extrapolation of these results to subjects using cannabis for therapeutic purposes will be discussed.

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DEVELOPING PER SE LAWS FOR DRIVING UNDER THE INFLUENCE OF CANNABIS (DUIC)

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Introduction: Jurisdictions in countries worldwide are adopting laws to address the traffic safety problem caused by drugged driving. Many of these laws are designed as per se laws with a zero tolerance for major illicit drugs. Zero tolerance laws consider drivers "impaired" if any measurable quantity of a listed drug or its metabolites is present in blood or other body fluids. While this approach facilitates law enforcement, it may unfairly classify many occasional drug users as impaired, even if they responsibly separate use and driving. This is a problem particularly with driving under the influence of cannabis (DUIC), i.e., marijuana and hashish. THC, the psychoactive constituent of cannabis, and its metabolites, may be detectable in blood and urine for days or even weeks after use. Per se laws specifying a science-based, finite legal limit for a suitable indicator of impairment by cannabis, would minimize this problem and motivate drivers to separate cannabis use and driving.

Method: An international working panel of physicians, forensic toxicologists and traffic scientists was assembled, to elaborate and offer recommendations for the development of a rational legal framework on DUIC. It reviewed current scientific evidence from experimental studies on the impairment of drivers by cannabis, epidemiological and culpability studies, the pharmacology of THC and issues related to drug testing and enforcement of DUI laws. Consensus positions on each of these areas were developed, critically reviewed, and finalized.

Results: Commonly consumed doses of THC may cause maximum psychomotor impairment in some behavioural areas comparable to that equivalent to a BAC of above 0.08%. Relevant acute effects typically subside within 3-4 hours after smoking. Particularly, epidemiological studies suggest that drivers under the influence of low doses of cannabis appear to be able to partially compensate for impairment. According to culpability studies, THC levels in blood serum below 5 ng/ml were not associated with an elevated accident risk. Even a THC serum level of between 5 and 10 ng/ml may not be associated with an above normal accident risk. Unless they are under the acute influence of the drug, both frequent and infrequent users of cannabis do not seem to have a higher accident risk than non-users. Despite its limitations, the THC level in blood serum is currently the most appropriate indicator of impairment by cannabis, while the presence of THC metabolites in blood or urine indicates past use but not present impairment. Current evidence suggests that a legal limit for THC in blood serum of 5–10ng/ml will effectively separate unimpaired drivers from those DUIC. Despite differences in pharmacokinetics between inhalation and oral use of cannabis, experimental studies suggest that a limit in this range is suitable for both routes of consumption. When selecting a numerical value, the risk of producing false positives and negatives, respectively must be balanced. A higher limit will result in a high proportion of false negatives, especially if the time lag between roadside detention and collection of a blood sample is long; a lower limit will increase the number of false positives. This would mainly affect regular cannabis users, which may present with THC serum levels of 2 ng/ml up to 48 hours after the last consumption of cannabis. Since concurrent use of alcohol and cannabis appears to increase accident risk, a lower limit for THC may be appropriate in that case.
Further studies will be required to strengthen the scientific basis for choosing a legal limit under per se laws for DUIC.

AN ENDOCANNABINOID HYPOTHESIS OF SUBSTANCE ABUSE

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After over four decades of intensive research on the brain reward pathways in the development and the compulsive use of addictive substances, the dopamine circuits and hypothesis remain a difficult area and perhaps a major problem and hindrance to progress in unraveling the biology of addiction (*Onaivi et al., Ann. N.Y.Acad. Sci. 2002: 965:28-46*). Pharmacological treatment of drug and alcohol dependency has largely been disappointing and new therapeutic targets and hypotheses are needed. As the usefulness of the pharmacotherapy of substance abuse has been limited, an endocannabinoid hypothesis is postulated from data from our studies and those of others. There is accumulating evidence indicating a central role of a previously unknown but ubiquitous endocannabinoid physiological control system (EPCS) in the regulation of the rewarding effects of abused substances. Endocannabinoids mediate retrograde signaling in neuronal tissues and are involved in the regulation of synaptic transmission, to suppress neurotransmitter release by the presynaptic cannabinoid receptors (CBrs). This powerful modulatory action on synaptic transmission has significant functional implications and interactions with the effects of abused substances. Additional support for the endocannabinoid hypothesis of substance abuse is derived from the action of cannabinoids or marijuana use on brain reward pathways that is similar to other abused substances. Further more administration of cannabinoids or the use of marijuana exert numerous pharmacological effects through their interactions with various neurotransmitters and neuromodulators.

Methods: Adult C57Bl/6 mice were evaluated in the elevated plus-maze test of anxiety following abrupt cessation from chronic treatment with selected doses of cocaine 1.0 mg/kg, diazepam, 1.0 mg/kg, ethanol, 8%w/v, methanandamide 10 mg/kg). In a separate group of this mice the ability of the CB1 cannabinoid antagonist, rimonabant, to block the withdrawal aversions of mice from alcohol and selected drugs with abuse potential was determined. We also used capsaicin (from hot pepper), a habit forming, food substance that is known to activate CBrs and vanilloid receptors (VR1rs) in the CNS, to study the involvement of the EPCS in the rewarding effects of capsaicin using mice. The interaction between vanilloid and cannabinoid system was performed using selected agonists and antagonists. The ability of the antagonist drug to block agonist drug effect was also evaluated in this paradigm.

Results: 1) Cannabinoid CB1 receptor antagonism reduced behavioral aversions following withdrawal from alcohol, cocaine, and diazepam. **2)** Treatment with capsaicin or WIN55212-2 induced in mice aversions to the open arms of the elevated plus-maze test. **3)** The aversive behavior induced in mice following treatment with capsaicin, which was dependent on gender and strain of mice used, was enhanced by pretreatment with WIN55212-2. **4)** Capsazepine, a VR1 antagonist reduced mouse aversions, while rimonabant, the CB1 antagonist, produced variable effects characterized by reduced aversions at low dose and increased aversions to the open arms of the plus-maze at higher doses. **5)** Both capsazepine and rimonabant blocked the aversions induced by WIN55212-2 and capsaicin, indicating a cross-talk between cannabinoid and vanilloid systems. **6)** Our data adds to data from other laboratories showing interaction of cannabinoids with the effects of nicotine and opiates which we extend to those of alcohol, cocaine and capsaicin.

Conclusions: We conclude from these findings that **a)** The differential sensitivities of capsaicin in the mouse strains which was gender specific, may indicate why some like hot "chili" peppers and others do not. This may be due to the interaction between the cannabinoid and vanilloid systems **b)** Cannabinoids therefore appear to be involved in adding to the rewarding effects of addictive substances including, cocaine and BDZs. **c)** These results taken together suggest that in the CNS the EPCS may be directly important natural regulatory mechanism for reward in the brain and also contribute to reduction in aversive consequences of abused substances. **d)** The existence and involvement of the EPCS in this *in vivo* model is presented as additional evidence that manipulating the EPCS could be exploited in reducing the behavioral consequences of withdrawal from alcohol and drug dependency.

SATIVEX ADVERSE EVENT PROFILE AND COMPARISON WITH MARINOL AND "MEDICAL GRADE CANNABIS" IN CLINICAL STUDIES

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Adverse events associated with recreational cannabis usage have been extensively reviewed in various studies. As clinical cannabis returns to the pharmacopoeia the question of side effects in the context of therapeutic usage of prescription cannabis is an important one that heretofore has been little investigated. The psychoactivity and side effect profile of Sativex oromucosal cannabis based medicine contrasts with that of smoked cannabis in recreational users because of differences in composition, dose and route of administration, pharmacokinetic parameters, and motivation of the user.

Although no direct head-to-head comparisons of Sativex to other agents have been performed, results of various randomised double-blind clinical studies were combined to assess adverse event profiles of Sativex with available studies of Marinol and "medical grade cannabis."

In regular usage, Sativex is associated with a low incidence of adverse events including dry mouth, dizziness, mouth soreness and tachycardia vs. placebo, many of which are transient upon initiation of therapy. Intoxication levels with Sativex are very low level and indistinguishable from placebo upon continued usage.

A comparison of results obtained with Sativex (Rog et al. *Neurology* 2005: in press) to Marinol (Svendsen et al. *Brit Med J* 2004; 2004; 329(7460):253) in treatment of central neuropathic pain in multiple sclerosis reveals evidence for greater efficacy for Sativex with lower adverse event profile despite higher average doses of THC employed. Similarly, a comparison of side effects of Sativex in long term safety-extension (SAFEX) studies in comparison to reports by users of medical grade cannabis utilised by patients in the programme of the Dutch Office of Medicinal Cannabis (Gorter et al. *Neurology* 2005; 64 (5):917-9) suggests much lower rates of treatment-related complaints for oromucosal administration of cannabis extract. Reasons for these differences will be discussed including: comparative pharmacokinetic profiles, synergy of therapeutic effects and reduction of sequelae by inclusion of cannabidiol, reduction of first-pass metabolism of THC to 11-hydroxy-THC, and elimination of pulmonary sequelae with Sativex.

Conclusions from this study are that Sativex represents an advantageous formulation and delivery system that maximises therapeutic benefits and minimises sequelae from cannabis based therapy.

Posters

CANNABINOIDS AS ANTISPASTIC AGENTS FOR MULTIPLE SCLEROSIS: A QUALITATIVE SYSTEMATIC REVIEW

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Spasticity is a common and disabling problem in multiple sclerosis (MS) that limits patients mobility and impairs normal daily functions. Antispastic drugs have shown limited efficacy. Preclinical antispastic data for cannabinoids in MS models are promising but there is controversy about its clinical usefulness. Objective: to assess the efficacy and tolerability of cannabinoids as antispastic agents for MS patients.

Method:

Design: systematic review of double blinded and randomised, controlled trials (RCTs).

Setting: electronic databases, PubMed, and Cochrane library and hand searches.

Exposures: cannabis or cannabinoids, nabilone, Δ^9-tetrahidrocannabinol (THC) or cannabis extracts.

Main outcome measures: objective and subjective spasticity scales and adverse effects. Validity of trials was assessed independently with the Jadad scale. Results: Seven trials (923 patients resistant to usual antispastic agents) were included. THC was assessed in four trials (705 patients, 244 exposed), nabilone in one trial (one patient) and a cannabis extract in four (900 patients, 364 exposed). All trials were controlled with placebo and only two were direct comparisons (THC *vs* cannabis extract). All trials except one had an escalating dose period. Cannabinoids were orally administered in six trials and by an oromucosal spray in one. Mean treatment duration was four weeks (ranging from three days to fifteen weeks). Efficacy outcome variables were heterogeneous. All trials assessed spasticity by subjective measures. Additionally, six trials assessed spasticity with an objective scale; four of which used the Asworth scale. Although cannabinoids produced no antispastic benefit compared to placebo when assessed by the Asworth scale, they improved subjective spasticity in six trials and objective spasticity in one. Cannabinoids were well tolerated. Patients or investigators identified the active treatment in most trials. Conclusion: In patients with spasticity due to MS, cannabinoids produce a subjective symptomatic improvement but have not shown any benefit effect when assessed with the Asworth scale, as the majority of other antispastic drugs.

SOLUBILIZING THC IN WATER BY CYCLODEXTRINS

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The solubility of THC in water is so low (about 1 ug/ml) that it is not practically possible to make an aqueous solution of THC available as laboratory standard or for clinical use. The use of water as solvent is preferred in cases like intravenous or inhaled preparations. Also water is more stable against evaporation in the case of quantified laboratory standards. The use of cyclodextrins for improving the watersolubility of THC by complexation has been mentioned briefly (Jarho *et al*. 1998). Cyclodextrins are cyclic sugar-compounds of various sizes that are widely used as solubilizing and stabilizing agents. They have a GRAS status and can be safely used for most applications, including clinical formulations. The goal of this study was to determine the physicochemical characteristics of a THC-CD complex and to test its suitability for further laboratory and clinical use.

Methods: several types of cyclodextrins (CD) were tested for complexation with THC over a range of CD concentrations up to 40% (alpha, beta, gamma and randomly-methylated-beta (RAMEB)-CD). The best performing one was further used for determination of a) the binding stochiometry by making a continuous variation plot, b) the orientation of the THC-molecule inside the complex by using ^{1}H-NMR- and NOESY-NMR techniques, c) effect of pH (range 5-9) on efficiency of complexation, d) stability of the complex up to 8 weeks at roomtemperature in the light, compared to a standard ethanol solution of THC. Quantification of THC solutions was done by quantitative NMR and HPLC. Suitability of the water-solution as quantitative HPLC or GC standard was determined by comparing expected vs. observed peak area after injection of a dilution range of the solution. The toxicity of the complex upon inhalation was tested using an in vitro ciliary beat frequency assay (Merkus *et al*., 2001). Finally the effect of CD-complexation on the water solubility of other major natural cannabinoids was determined.

Results: only the use of RAMEB resulted in a significant increase of the watersolubility of THC to about 10 mg/ml for a 40% CD-solution. ^{1}H- and NOESY-NMR measurements showed a 2:1 complexation of THC with RAMEB. Interaction of THC with RAMEB was mainly through the aliphatic sidechain (C-5) and phenolic ring. Changing pH in the range of 5-9 had no effect on the efficiency of complexation. Complexed THC in a water solution showed no degradation after 8 weeks at roomtemperature in light, although some microbial growth was observed. Use of the complex solution as quantitative HPLC or GC standard was found to be possible, but a significant cytotoxicity on ciliary cells of chicken embryos was observed. Finally all tested cannabinoids showed an increased water solubility after complexation with RAMEB.

Conclusion: complexation of THC with the cyclodextrin RAMEB increases its watersolubility to a level (milligrams/ml) that makes it practical for use in clinical preparations or as a water-based laboratory standard. As CD's are sugars, the solution should be sterilized for use because of easy microbial contamination. Unfortunately the THC-RAMEB complex displayed a significant cytotoxicy for ciliary cells, possibly complicating the use of this complex in an inhalable THC preparation. Complexation with RAMEB seems to be promising also for other cannabinoids.

CANNABINOIDS EXERT POTENT ANTI-PROLIFERATIVE EFFECTS ON HUMAN BREAST CANCER CELLS

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Breast cancer is one of the most common forms of malignancy diagnosed in women. Research suggests cannabinoids may be effective in the palliative care of cancer patients. Furthermore, cannabinoids may have direct anticancer potential with studies showing that they inhibit the proliferation of numerous cancer cell lines. The endocannabinoid, anandamide, has anti-proliferative actions in human breast cancer cell lines via a cannabinoid CB_1 receptor mediated pathway *(De Petrocellis et al. Proc. Natl. Acad. Sci. USA 1998; 95;8375-8380)*. The current project aims to test whether the plant-derived cannabinoid, cannabidiol (CBD) and the synthetic cannabinoid, WIN 55,212-2 have anti-proliferative effects on the MCF-7 epitheloid human breast cancer cell line.

Methods: MCF-7 cells were incubated for 4, 24 and 72 h in the absence or presence of increasing concentrations of WIN 55,212-2, CBD or the traditional anticancer agents, mitoxantrone and etoposide. Cell viability was assessed using the MTS assay. The effect of cannabinoids on the cell cycle was examined using propridium iodide (PI) staining and flow cytometry. The role of cannabinoid or vanilloid receptors in the anti-proliferative effects of cannabinoids was investigated by incubating the cannabinoids in the absence or presence of the CB_1 receptor antagonist, AM 281 (1-10 μM), the CB_2 receptor antagonist, SR 144528 (0.5–5 μM), the VR_1 receptor antagonist, capsazepine (1-10 μM), or a combination of all three antagonists.

Results: The MTS assay showed that both CBD and WIN 55,212-2 inhibit the proliferation of MCF-7 cells only after a 72 h exposure. WIN 55,212-2 was effective at picomolar concentrations (IC_{50} = 170 pM) and was more potent than the traditional cytotoxic agents mitoxantrone (IC_{50} = 32 nM) and etoposide (5 nM). CBD was effective at nanomolar concentrations (IC_{50} = 61 nM). Preliminary experiments using PI staining combined with flow cytometry showed that WIN 55,212-2 and CBD appeared to promote a cytostatic action by arresting the cell cycle in the S/G2 phase. The anti-proliferative effects of both CBD and WIN 55,212-2 were significantly, but not completely reversed, by AM281, SR 144528 and capsazepine. Interestingly, a combination treatment of all three antagonists completely reversed the reduction in cell viability observed with either WIN 55,212-2 or CBD.

Conclusions: WIN 55,212-2 has potent anti-proliferative effects on a human breast cancer cell line. The non-psychoactive cannabinoid, CBD also inhibits the proliferation of these cells, albeit at higher concentrations than two traditional cytotoxic agents. The effects of WIN 55,221-2 and CBD appear to be mediated by a combination of CB_1, CB_2 and VR_1 receptors. These anti-proliferative actions appear to be cytostatic in nature, with the cannabinoids causing cell cycle arrest in S/G2 phase. However, further experimentation is needed to expand upon these findings. Taken together, these results provide additional support for the development of cannabinoids as novel treatments for breast cancer.

WIN 55,212-2 VERSUS KETAMINE IN A PERIPHERAL NEUROPATHY INDUCED BY PACLITAXEL

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Introduction: Paclitaxel is an effective antineoplastic agent in the treatment of solid tumours that produces a dose-limiting painful peripheral neuropathy in a clinically significant number of cancer patients.
It is well known that agonists of the cannabinoid receptor are able to reduce hyperalgesia and allodynia after nerve injury.
The **aim** of our study is to compare the analgesic effect of ketamine, an NMDA receptor antagonist and WIN 55,212-2 (WIN), a cannabinoid agonist, in an animal model of peripheral neuropathy induced by paclitaxel in rats (Polomano et al., Pain 2001; 94:293-304).

Material and methods: Paclitaxel (1mg/kg) was administered intraperitoneally (i.p.) on four alternated days (Days 1, 3, 5 and 7). The plantar surface of the hind paw (sciatic nerve territory) was tested (day 21) for thermal-hyperalgesia and mechano-allodynia. Thermal-hyperalgesia was tested using method described by Bennett and Hargreaves, (1990) and mechano-allodynia was assessed with the von Frey filaments (Tal and Bennett, 1994). Drugs were administered on day 22.

Results: Paclitaxel produced a statistically-significant thermal hyperalgesia (- 30% of threshold temperature) and mechano-allodynia (-70% of threshold pressure) in both hind paws. There are no left-right differences.
WIN 1 and 1.5 mg/kg i.p. significantly reduced hyperalgesia (+12% and +13% of the threshold temperature*)* and allodynia (-25% and + 22% of the threshold pressure).
Ketamine 25 and 50 mg/kg i.p. only reduced allodynia (-38% and +4%) whereas hyperalgesia was not affected.

Conclusions: Although more work is required, these data can suggest that WIN 55,212-2 is more potent than ketamine reducing hyperalgesia in this model of peripheral neuropathy induced by paclitaxel.

INTERACTION OF THE GENERAL ANAESTHETIC PROPOFOL AND SELECTIVE AGONISTS FOR CANNABINOID-RECEPTOR TYPE 1 AND 2.

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Introduction: It has been shown in numerous studies that Δ9-THC and other cannabinoids possess analgesic, sedative and immunmodulatory effects. At least, two different G-protein-coupled cannabinoid-receptors (CB) have been identified (De Petrocellis et al., Br J Pharm 2004; 141: 765-774). Could a combination of selective CB-agonists with intravenous anaesthetics be favourable in the perioperative setting? The purpose of this study was to establish an animal model monitoring analgesic and sedative effects of propofol combined with selective agonists for the CB-receptor type 1 and 2.

Methods: With approval at the local animal care committee twenty SV-129 male mice received intraperitoneal injections (10 µl/g) of propofol, the CB1-agonist ACEA and the CB2-agonist JWH133. Analgesia was determined by tail flick with a cut-off time after 10 s of exposure. Sedation was monitored by a rotating rod with a diameter of 3 cm and 16 rotations per min. A cut-off time of 60 s was defined as no sedation.

Results: The maximal sedative effect of propofol (50 µg/g) was observed with 53 s on the rotating rod after 2.5 min, and sedation was diminished 7.5 min post injection. Propofol had no effect on tail flick. ACEA and JWH133 alone had no effect on sedation after injection of 5 µg/g, respectively. The maximal analgesic effect of ACEA occurred at a tail flick latency of 8.8 s, and of JWH133 at a tail flick latency of 7.9 sec after 10 min compared to baseline latency of 3.9 s, respectively. The effects diminished slowly over 10 h.
The sedative effect of propofol combined with ACEA was significantly increased with a mean running time of 1.9 s on the rota rod after 5 min and an offset after 45 min, but propofol combined with JWH133 did not demonstrate any additive effect. Analgesic effects of ACEA and JWH133 were not influenced by the combination.

Conclusions: ACEA and JWH133 alone, as well as combined with propofol, produce analgesic properties in the tail flick model showing a rapid onset and a long lasting effect, respectively. Sedative action and duration of propofol significantly increased in presence of ACEA, but not in presence of JWH133. Propofol affects endocannabinoid function by inhibition of fatty acid amide hydrolase (FAAH) (Patel et al., Br J Pharm. 2003; 139: 1005-1013). As metabolism of ACEA is FAAH-independent, the pharmacological basis for the synergism of the CB1-agonist on propofol's sedation is currently not known.

CANNABINOID MODULATION OF P-GLYCOPROTEIN EFFLUX ACTIVITY AND EXPRESSION

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The analgesic, anti-emetic and appetite stimulant qualities of cannabinoids have justified their use as palliative care agents for patients receiving anticancer treatment. The effectiveness of anticancer treatment is influenced by the ability of tumour cells to develop resistance to chemotherapeutic agents. The most extensively characterized mechanism of resistance is that mediated by the ATP-binding cassette transporter, P-glycoprotein (P-gp), which acts to efflux a diverse range of clinically employed anticancer agents. Previously it has been reported that plant-derived cannabinoids are capable of reversing P-gp mediated efflux of the fluorescent substrate rhodamine 123 (Rh123) *(Molnar et al., Anticancer Research. 2000; 20: 861-7).* We have characterized the effect of the plant-derived cannabinoids, cannabidiol, (CBD), cannabinol (CBN) and delta-9 tetrahydrocannabinol (THC) on P-gp efflux activity and expression in human leukaemia cells that over-express P-gp as a result of repeated exposure to vinblastine (CEM/VLB_{100} cells).

Methods: 1) The accumulation of P-gp substrates was assayed in the presence of cannabinoids and after **2)** pre-incubation for 72 h. **3)** The cytotoxicity of vinblastine in the presence of sublethal concentrations of cannabinoids was assessed using the MTS/PMS metabolic assay. **4)** P-gp expression after 72 h incubation with cannabinoids was assessed using western blot analysis.

Results: i) Sublethal concentrations of CBN, CBD and THC promoted a small decrease in Rh123 accumulation in CEM/VLB_{100} and *MDR1* transfected mouse 77.1 fibroblast cells compared to vehicle treated controls. **ii)** CEM/VLB_{100} cells pre-incubated with CBD and THC showed increased Rh123 accumulation compared to cells pre-incubated with vehicle. **iii)** CBN, CBD and THC reversed the reduced sensitivity of CEM/VLB_{100} cells to vinblastine-induced cytotoxicity. **iv)** 72 h exposure of CEM/VLB_{100} cells to CBN and THC reduced the amount of P-gp expression in crude membrane extracts.

Conclusions: We conclude from these findings that the cannabinoids assayed do not directly inhibit P-gp mediated substrate efflux. Long-term exposure to cannabinoids produces a functional decrease in efflux activity, which may account for the increased toxicity of the P-gp substrate, vinblastine when co-administered with subtoxic doses of cannabinoids. This decreased efflux activity in cells exposed to cannabinoids for a prolonged period is due to down-regulation of P-gp expression. This study suggests that cannabinoids may be safely used as palliative care agents in patients receiving chemotherapy treatment as they do not enhance P-gp-mediated drug resistance. Indeed, cannabinoids may modestly improve the efficacy of P-gp substrates by decreasing P-gp expression. Further research into cannabinoid modulation of other multiple drug resistance mechanisms responsible for anticancer drug resistance is required.

ADD-ON DELTA-9-TETRAHYDROCANNABINOL (THC) IS INEFFECTIVE IN DRUG-RESISTANT RESTLESS LEGS SYNDROME (RLS)

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Background: Restless Legs Syndrome (RLS) is a well described neurologic disorder with a prevalence of up to 10% in a normal population. Diagnostic criteria are: (i) urge to move the limbs, usually with unpleasant sensations, (ii) worsening during rest, (iii) relieve by movements, (iv) worse in the evening or at night. Delta-9-tetrahydrocannabinol (THC) is used in form of Cannabis cigarettes by many RLS patients because they experience a positive effect on the typical subjective sensory disturbances particularly in the resting conditions, in the evening, and at night.

Methods: In a pilot study we have tested in a randomized, double-blind, placebo-controlled, crossover design the effect of 15 mg oral THC (dronabinol, Marinol®) in 6 patients with drug-resistant RLS taken "add-on" with the regular dopaminergic or opioidergic treatment. Only cannabis-naïve patients were included. Subjective and objective measurements were obtained from the suggested immobilization test (SIT) as well as from the subsequent all night-video-polysomnography.

Results: THC did not show any significant effects on subjective complaints (visual analogue scale) and objective measurements (smoothed rectified EMG from anterior tibial muscle) during the SIT compared to placebo. No effect was found either on sleep latency, sleep efficiency, and periodic leg movements in sleep (PLMS-Index) during the all-night video-polysomnography. Side effects such as mild nausea, dizziness, pleasant relaxing feelings, horror dreams or intensive color visions were reported by 5 of the 6 patients after THC but not placebo.

Conclusions: We conclude that oral "add on" THC in a dosage leading to noticeable side effects did not influence positively symptoms and signs in drug resistant RLS. More studies are needed to explain whether the negative result is due to the exclusion of cannabis-experienced patients or to relevant pharmacokinetic differences between the oral formulation and the cigarettes.

CANNABINOID-1 RECEPTOR FUNCTIONING WITHIN THE ASCENDING PERISTALTIC REFLEX: NEW ELECTROPHYSIOLOGICAL TOOLS TO INVESTIGATE THE SPATIAL NEURONAL PROJECTIONS

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Background: Propulsion along the intestine appears to occur by the action of a series of local reflexes which cause oral contraction and anal relaxation of circular muscle. This is associated with typical electrophysiological changes in membrane potential as result of different excitatory and inhibitory pathways.

Aim: Aim of the study was to investigate influence of local electrical field stimulation (EFS) on gastrointestinal electrophysiology of murine large bowel using a 12 channel stimulation electrode in a newly designed model of the ascending peristaltic reflex with simultaneous intracellular recording.

Methods: Isolated proximal colon without mucosa and submucosa was investigated. Reflex responses were initiated by EFS (12 electrodes (SE) 1 mm wide and 0.45 mm apart from each other) and excitatory (EJP) and inhibitory (IJP) junction potentials were recorded from circular smooth muscle cells by intracellular recording.

Results: Under basal conditions circular smooth muscle cells displayed a stable resting membrane potential (–56.7±6.9mV, n=13). EFS (single pulses with 0.3ms duration; 15V) elicited TTX-sensitive, neuronal induced EJP (cholinergic, atropine-sensitive) and IJP (biphasic: fast (fIJP, apamin-sensitive) and slow (sIJP, nitrergic, LNNA sensitive)) which showed distance-dependency and specific characteristic responses dependent on the distance between stimulation and recording site. The EJP was maximal when stimulation-site SE6/7 was used (141±34 % compared to SE1). A wave like EJP can be recorder over the different SE resulting in a maximal EJP at SE 6/7 and a maximal projection distance of 17 mm. Both components of IJP were maximal during direct stimulation (SE1) and gradually decreased to SE7. EFS at distances more than 8 mm apart do not produce IJP. The specific CB-1 receptor agonist WIN 55,212-2 concentration dependently reduced amplitude of EJP and IJP and cause an “oral-shift” of the ascending part of peristaltic reflex demonstrating the involvement of CB1-receptors by influencing neurotransmission and reflex-timing.

Conclusions: Spatial projections of neurones within the peristaltic reflex can be determined by using an electrophysiological setup with multiple stimulation sites along the colon. Thereby excitatory neurones project maximally 17 mm, whereas inhibitory neurones project maximally 8 mm. Electrophysiological junction potentials and spatial functioning of the peristaltic reflex are modulated by the cannabinoid-1 receptor.

I-124-AM281 PET IMAGING OF CB1-RECEPTORS IN SCHIZOPHRENIA: A CASE STUDY

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Introduction: There are different lines of evidence indicating that the central cannabinoid CB1-receptor system has a pathophysiologic relevance in schizophrenia. 1.) Several studies reported an increased incidence of schizophrenia in young people exposed to cannabis compared to non users. 2.) Perception abnormalities induced by Δ^9-tetrahydrocannabinol in normal volunteers are similar to those observed in schizophrenia. 3.) Endogenous cannabinoids have been found to be elevated in the cerebrospinal fluid of schizophrenic patients. 4.) There is evidence for an increased binding capacity of CB1-receptors in the anterior cingulate cortex in schizophrenic patients. In a recent study, we were able to investigate the central CB1-receptor system using the inverse agonist AM281 labelled with Iodine-123 (I-123) and single photon emission computed tomography (SPECT*)* in patients with Tourette syndrome. However, in vivo positron emission tomography (PET*)* studies of this system in humans are lacking. The purpose of this study was to explore, whether imaging with AM281 labelled with I-124 and PET might provide superior results. Therefore, we studied the central cannabinoid receptor system in a patient suffering from schizophrenia.

Methods: We investigated a 47 years old right handed patient with schizophrenia who was initially referred for a psychiatric assessment at the age of 33 because he had experienced aural hallucinations, persecutory delusions and impaired social contacts during the previous five years. During the last 4 years the patient was stabilized. For several years he was treated with different neuroleptics, at the time of PET scanning his medication was Amisulprid 300mg/d and Carbamazepine 800mg/d. His premorbid intelligence and personality profile were unremarkable. He had never smoked cannabis.
In a scientific individual experiment approved by the local ethics committee the patient was injected with 50 MBq I-124-AM281 (N-(morpholin-4-yl)-1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-1H-pyrazole-3-carboxamide). Dynamic PET data (ECAT HR+, Siemens, Erlangen, Germany) and simultaneous blood samples were obtained over 90 min. A three dimensional parametric map of distribution volume (DV) was generated by the classical Logan plot using the PMOD software (University Hospital Zurich, Switzerland). The 3D map was transferred into the sterotactic standard space according to MNI (Montreal Neurological Institute) using SPM99 software (Wellcome Department of Cognitive Neurology, London, UK) with the standard template for blood flow. DV in multiple brain regions was read out using the Anatomical Automatic Labeling (AAL) program (Neurofunctional Imaging Group, Cyceron, Caen, France). Ratios of DV were calculated for all regions as measure of specific binding, with white matter as reference.

Results: Clearly pronounced uptake could be delineated in the region of the striatum and the globus pallidus. Accordingly the highest DV-ratios were detected in the putamen (1.37) and the pallidum (1.35). Moderately high ratios were detected in the cerebellum (1.16) and the anterior cingulate (1.15).

Conclusions: The pattern of I-124-AM281 uptake is in accord with the known distribution of CB1-receptors in man. Quantitative parameters seem to surpass those obtained on average with the SPECT ligand. This suggests that the PET ligand might be even more promising for imaging of this receptor system. Nevertheless, due to the limited image contrast and the relatively high radiation exposure further tracer development is necessary.

INTERACTION BETWEEN CANNABINOID SYSTEM AND OREXIN A IN FEEDING REGULATION

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The cannabinoid system is involved in feeding regulation through the CB1 receptor, a G protein-coupled receptor (GPCR). The lateral hypothalamus has high levels of CB1 and endocannabinoids such as anandamide and 2-araquidonyl glycerol, which promote overeating in partially satiated rats. Rimonabant is one of the most potent and selective central cannabinoid (CB1) receptor antagonists. It antagonizes the hyperphagia induced by cannabinoids and elicits a dose-dependent reduction of food intake in food-deprived rats and partially satiated rats, which suggests that CB1 antagonists could be useful as appetite suppressant drugs. A biochemical interaction between CB1 and OXR1, a orexin receptor, has been found in a recent *in vitro* study. Furthermore, CB1 and OX1R receptors are co-expressed in the lateral hypothalamus
For further investigation of the *in vivo* interaction between orexin A and cannabinoids in feeding behavior, we have studied: (1) the effect of peripheral administration of rimonabant, (2) the effect of central administration of orexin A and (3) the effect of combined administration of rimonabant and orexin A, all in pre-fed animals.

Methods: Male Wistar rats were used in two groups. In the first one, the acute effect on feeding of three different doses of *i.p*. rimonabant was measured. In the second group, rimonabant (1mg/kg) was injected *i.p*. and, 10 min later, orexin A was injected *i.c.v.* in pre-fed rats. Food intake was measured every 60 min for 240 min. Body weight and water-intake was measured before test and 240 min afterwards.

Results: 1) Systemic administration of the selective CB1 antagonist Rimonabant reduced food intake, water intake and body weight 2) administration of orexin A increased feeding in pre-fed animals at 60 min after icv injection at every dose and 3) Rimonabant blocked the effect of orexin A on food and water intake in partially satiated rats.

Conclusions: this research studies the connections between the endocannabinoid system and orexin A *in vivo* for the first time. The results obtained provide evidence of the existence of a relationship between them and confirm the *in vitro* results of Hilairet et al. (*J. Biol. Chem. 2003;*278:23731-23737). Rimonabant blocks the orexigenic effect of orexin A and it is a new therapeutic target of different feeding diseases.

PRELIMINARY DATA FROM AN ONGOING SURVEY ON THE THERAPEUTIC USE OF CANNABIS IN ITALY

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Introduction: in November 2003, ACT started a survey to collect information on the medical use of cannabis derivatives in Italy. The survey targeted both the users of natural derivatives, still illegal in our country, as well as the users of synthetic derivatives, unavailable on the market but obtainable through a cumbersome importation process from other European countries.

Methods: data were collected through an anonymous questionnaire sent to ACT members and downloadable to all interested patients on our association's site www.medicalcannabis.it.

Results: 70 questionnaires were filled by the patients (38 males, 32 females; average age 36 years). The oldest participant was 87, the youngest less than 2 year-old. Remarkably, 12 patients were of paediatric age.
The most frequent conditions in this first group of patients were the following: multiple sclerosis (21 patients), epilepsy (17 pts) and chronic pain (13 pts , of whom 3 affected with rheumatoid arthritis, 2 with migraine, 1 each with phantom limb syndrome, vertebral collapse from osteoporosis, post-traumatic osteoarticular pain, IV stage haemorrhoids, chronic arachnoiditis, post-mielitis neuropathic pain, gastro-esophageal pain, Camurati-Engelmann disease). In addition, 5 patients reported to use cannabis to treat chemotherapy-induced nausea and vomiting, 5 to be affected with marrow lesion-induced spasticity, 3 with depressive syndrome, 2 with AIDS-related wasting syndrome, 2 with insomnia, 1 with spasticity as a sequel of brain ischaemia, and 1 with bronchial asthma.
42 patients reported to use "raw" cannabis (hashish and/or marijuana) acquired either in the black market (20 patients), or self-grown (10), or both (12). 14 patients used a natural CBD extract, obtained from plants of a legally authorized plantation. Finally, 12 patients used a synthetic derivative legally imported from abroad.
A low incidence of side effects was reported: in 36 cases there were no notable side effects at all, in 33 cases only minor side effects were reported, while only in 1 case side effects were considered serious enough to justify a discontinuation of the therapy. Among the side effects it should be pointed out that 9 patients suffered legal problems related to the use of "illicit" cannabis.
Survey responders spent about 170 Euros per month on average. One patient mentioned excessive cost of treatment as the main reason for its discontinuation.
In most cases, therapy with cannabis derivatives took place under medical surveillance. 31 patients reported they were followed by a specialist, 10 by a general practitioner. 29 patients, however, were not referring to any medical professional.
Finally, 71% of the patients reported that they had not used cannabis before falling ill.

Conclusions: data emerging from the analysis of this first sample of italian medical cannabis users present both resemblances with similar surveys conducted in other countries, as well as features that can be considered specific for the italian reality. Further data will be collected to complete the survey and improve our knowledge on the therapeutic use of cannabis in Italy.

PILOT CLINICAL TRIAL PROTOCOL TO EVALUATE PRELIMINARY EFFICACY AND TOLERABILITY OF A CANNABIS MEDICINAL EXTRACT IN PATIENTS WITH CHEMOTHERAPY INDUCED NAUSEA AND EMESIS.

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Introduction: Chemotherapy induced nausea and vomiting remains a clinical problem. Around 40% of individuals receiving moderately emetogenic drugs, such as doxorubicin and cyclophosfamide have delayed nausea or vomiting despite antiemetic treatment with serotonin receptor antagonists and/or dexametasone and metoclopramide. Cannabinoids such tetrahidrocannabinol (THC) and cannabidiol (CBD) have shown antiemetic and antinausea properties in preclinical studies. On the other hand, a systematic review suggested that THC was a more effective antiemetic drug than prochlorperazine and metoclopramide in patients receiving moderately emetogenic chemotherapy[1]. However, there is no information on the efficacy of cannabinoids compared to the current reference treatment of this chemotherapy side effect.

Objective: To describe the protocol of a pivotal clinical trial to evaluate preliminary efficacy and tolerability of a cannabis medicinal extract self-administered as an oromucosal spray added to standard treatment for the prevention of delayed emesis induced by moderately emetogenic cancer chemotherapy.

Methods: A pilot, randomised, double blinded, parallel and placebo controlled clinical trial with 60 patients with resistant nausea and/or vomiting induced by the first moderately emetogenic chemotherapy cycle is proposed. The study will be conducted in the hospital outpatient clinic, but patients will take the treatment at home. The first aim of the study is to determine the antiemetic and antinausea efficacy of an individualized dose of a whole-plant cannabis extract added to the standard treatment for the prevention of nausea and vomiting induced by moderately emetogenic chemotherapy during the first 120 hours. As a second aim toxicity, well being, opioids need, pharmacokinetic parameters and patient and doctor satisfaction will be assessed. Tolerability to the treatment will be monitored diary by phone during treatment days 1 to 5..

Results: Data from an observational study[2] and a systematic review[1] supports the hypothesis that the antiemetic efficacy of the cannabis extract will be superior than that of placebo.

Conclusion: Data from this pilot study is needed to assess the relevance of a future phase III clinical trial.

1. BMJ 2001; 323: 16-21 .
2. Med Clin (Barc) 2005; 124:78-9.

THERAPEUTIC POTENTIAL OF CANNABINOIDS

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Advances in the comprehension of the mechanisms of action of THC and other cannabinoids over the past 15 years have revived their therapeutic interest. This review presents the most current information on the therapeutic potential of cannabinoids.

Method : A systematic search was performed in Medline (PubMed), until April 1st 2005. Key words used were cannabis, marijuana, marihuana, hashish, hashich, haschich, cannabinois, tetrahydrocannabinol, THC, dronabinol, nabilone, levonantradol, randomised, randomized, and human. The search included reports and review articles in english, french and spanish. For the final selection, only well-controlled clinical trials were considered.

Results: 69 clinical studies evaluating the therapeutic effects of cannabinoids were identified. For each clinical trial, the host country, the number of patients involved, the type of study and comparisons performed, the products and doses used, their efficacy and their adverse effects are described. Cannabinoids present an interesting therapeutic potential as antiemetics, appetite stimulants in debilitating diseases (cancer and AIDS), analgesics and in the treatment of multiple sclerosis, spinal cord injuries, Tourette's syndrome, epilepsy and glaucoma.

Conclusion: The therapeutic future of cannabinoids is promising. For each pathology where controlled clinical trials have demonstrated encouraging results, it remains to determine what type of cannabinoid and which route of administration are most suitable to maximize the efficacy of each preparation and minimize the incidence of undesirable reactions.

CEREBROSPINAL DELAYED ALLERGIC REACTION TO PESTICIDE RESIDUE

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A 45 year old female medical cannabis club proprietor for the past ten years was trimming cannabis bud. Two years ago she noted break out with itchy rashes on her skin. after contact. She wore long sleeves to avoid contact.
She experienced severe sneezing episodes 18 months ago after trimming in an unventilated room. She avoided contact for 7 months, but resumed 10 months ago, she began to experience episodes of laryngospasm, eyelid twitching, sinusitis, rhinitis, and congestion for five months with increasing severity until admission to hospital 12-31-2004 with extreme weakness, 20 Kg weight loss, neuropathic pain, hemiplegia, and dysarrthria. Evaluation for tumor, infection, or vascular abnormality was completely negative. When confronted, the grower whom she had obtained the cannabis for many years admitted to the use of Avid (avermectin), a miticide of an unusual composition of a glycoside rather than usual organophosphate. She was hospitalized for 47 days. 29 days on an acute medical ward with 18 days in rehabilitation. At this writing her right-sided weakness and dysarrthria are resolving.

Treatment intervention included prednisone in decreasing dose, opioids, neurontin, vaporized and oral cannabis.

IN VITRO CYTOTOXICITY OF FOUR CANNABINOIDS (THC, THC-ACID, CBD, AND CBN) IN A PANEL OF SIX CANCER CELL LINES.

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Objective: In past years, the question has been raised whether (syntheticallyderived) cannabinoids and their derivatives can be used to develop new anticancer therapies. Indeed, certain cannabinoids are reported to have anti-tumor properties in cell lines and mouse models. The objective of this study was to determine the *in vitro* cytotoxicity of four cannabinoids isolated from *Cannabis sativa* L., i.e. delta-9-tetrahydrocannabinol (THC), delta-9-tetrahydrocannabinol acid (THC-acid), cannabidiol (CBD), and cannabinol (CBN), using the microculture sulforhodamine B (SRB) assay. A panel of six different human tumor cell lines was used: the WIDR (colon cancer), the M19 MEL (melanoma), the A498 (renal cell cancer), the IGROV (ovarian cancer), the H226 (non-small cell lung cancer), and the MCF-7 (breast cancer) cell line.
Methods: All cell lines were maintained in RPMI 1640 medium containing Hepes and phenol red, supplemented with 10% FCS, penicillin, and streptomycin. About 2,000 cells per well in a volume of 150 µL were plated in 96-wells flat-bottom microtiter plates. The plates were preincubated for 48 hours at 37^0 C in a humidified atmosphere containing 8.5% CO_2. Subsequently a three-fold dilution series of ten steps was made in complete medium for each cannabinoid tested. Stock solutions of each cannabinoid (98-99.5% purity, dissolved in ethanol) were dilutedin complete medium to a start concentration of 250 µg/mL. Of each dilution 50 µL was added to the well containing the cells after 5 days, the incubation was terminated and the cells were fixed with 10% trichloroacetic acid in PBS. After washing, the cells were stained with 0.4% SRB dissolved in 1% acetic acid after which the staining solution was further diluted by 150 µl 10 mM Tris-base. Staining was quantified by measuring the absorbance at 540 nm using a microplate reader. Average data based on quadruplicate measurements were used to calculate concentration-response curves and to determine the ID_{50} values (the concentration cannabinoid producing 50% inhibition of growth) using Deltasoft 3 software.
Results: THC and CBN were found to have a low to moderate cytotoxicity (ID_{50} 2,500 – 20,000 ng/mL). Surprisingly, THC-acid shows moderate to high cytotoxicity (ID_{50} 250 – 2,500 ng/mL) for the melanoma cell line, whereas CBD can be classified as moderately to highly cytotoxic for the ovarian cancer cell line in particular. The average ID_{50} values of the four cannabinoids *in vitro* using the SRB cytotoxicity assay are given in Table 1.
Conclusions: Compared to THC and CBN, THC-acid, and CBD show relatively high *in vitro* cytotoxicity in the melanoma and the ovarian cancer cell line, respectively. These results warrant further investigations of the cell growth inhibiting potential of these two substances in these and other cell lines, especially as both compounds are known to be psychomimetically inactive. As cannabinoids clearly have cytotoxic potential, other isolated cannabinoids should also be scanned for their cytotoxic potential. However, caution is needed before implementing these results in clinical practice, as tumor growth induction by cannabinoids has been reported as well. Currently, we are developing a research program investigating the therapeutic potential of cannabinoids for the treatment of cancer.

Table 1. ID50 values (ng/mL) of four cannabinoids in vitro using SRB as cell viability test.

	A498	H226	IGROV	M19	MCF-7	WIDR
THC	8,416	8,393	6,451	3,184	7,703	8,155
THC-acid	8,886	9,475	10,391	**744**	4,195	8,458
CBD	5,808	3,223	**715**	2,093	1,796	2,376
CBN	9,755	9,565	11,035	8,473	8,814	9,993

Δ^9-THC AND OTHER CANNABINOIDS CONTENT OF CONFISCATED MARIJUANA: POTENCY TRENDS, 1994-2004

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The National Center for Natural Products Research (NCNPR), Research Institute of Pharmaceutical Sciences (RIPS), at the University of Mississippi has had a contract with the National Institute on Drug Abuse (NIDA) to carry out a variety of research activities dealing with marijuana for over 35 years. One of these activities (the Potency Monitoring [PM] program) is designed to provide analytical data relative to the potency of confiscated marijuana seized in the US. This involves seizures of both domestic origin and non-domestic origin. In previous communications we have reported on potency trends since the inception of the program in 1968 with the last report covering the period ending in 1997.

This report will provide data for the last ten years on approximately 30,000 cannabis samples (of which approximately 10,000 samples are of known domestic origin), 207 hashish samples, and 86 hash oil samples.

The data show that there was an upward trend in the average THC content of confiscated marijuana which increased from 3.48% in 1994 to 7.08% in 2004, over 100% increase. For hashish samples, there was no consistent increase from 1994 to 1999. However, the average potency of hashish samples increased from 4.16% THC in 2000 to 11.2% in 2004. No potency trends were observed for hash oil samples. It is interesting, however, to note that while hashish is prepared from intermediate-type cannabis (moderate THC and CBD content), hash oil is prepared from drug-type cannabis (high THC, low CBD content). It is also interesting to note that the upward trend in the potency of cannabis (marijuana) is not because of the increase in the potency of domestic samples but rather because of the increase in the potency of the non-domestic samples.

There was no trend or even much of a change in the average levels of the other cannabinoids (CBD, CBC, CBG, and CBN) in the cannabis samples over the reported time frame.

The breakdown of the potencies by type of preparation will also be presented.

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Research Contracts with the National Institute of Drug Abuse (NIDA) supported this work.

THE ENDOCANNABINOID SYSTEM AND CYSTIC FIBROSIS CFTR$^{-/-}$ MICE: A LOOK AT OSTEOPOROSIS AND SEX DIFFERENCES AS REVEALED BY CANNABINOID ADMINISTRATION

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Introduction: Cystic fibrosis (CF) is the most prevalent lethal autosomal recessive disorder in the Caucasian population, affecting 1 in 2500 newborns. The major symptoms of CF include severe lung and pancreatic disease, digestive disorder and excessive inflammatory response. Osteoporosis develops in at least 30% of CF patients. Recent evidence points at a regulatory role for the endocannabinoid system in bone development. Moreover, impaired fatty acid balance, which potentially regulates endocannabinoid synthesis, has been proposed as a major factor in CF etiology. Thus we have hypothesized that a dysfunctional Endocannabinoid CB Receptor (ECBR) may be found in CF patients and that administration of cannabinoids may improve the health status of CF patients.

Methods: Daily Δ^9-THC injections (5mg/kg, from day 7 till day 28) were performed in animal model for cystic fibrosis (cftr-deficient mice, cftr$^{-/-}$). Cannabinoid-related behaviors, survival, weight increase and bone structural parameters were recorded throughout development. We have also compared the effects of acute administration of the cannabinoid receptor agonist HU-210 (0.004 mg/kg), on the behavior and physiologic functions of adult cftr$^{-/-}$, cftr$^{+/-}$ and cftr$^{+/+}$ mice. Behavior was tested in the "tetrad" (a series of assays, which reflect cannabinoid-like effects).

Results: 1. Chronic daily Δ^9-THC injections did not significantly improve survival and weight gain in cftr$^{-/-}$ mice; moreover, cftr$^{-/-}$ males treated with Δ^9-THC showed a considerable <u>decrease</u> in weight gain compared to the controls. Body weights of wild type mice were transiently increased during Δ^9-THC treatment.
2. Acute HU-210 administration significantly decreased motor activity in <u>males</u> (both cftr$^{-/-}$ and controls), but not in females; body temperature was significantly decreased only in cftr$^{-/-}$ mice (males and females); intestinal motility almost ceased in both cftr$^{-/-}$ and controls (males and females).
3. No differences in any bone parameter were found between untreated cftr$^{-/-}$ and *wildtype* mice, at 1 week of age. Bone structure at older ages in mice, with or without chronic treatment with Δ^9-THC, is currently under investigation.

Conclusion: Cannabinoid-mediated regulation of body temperature is impaired in cftr$^{-/-}$ mice. In males the impairment of the endocannabinoid system is demonstrated also during infancy as increased vulnerability to Δ^9-THC (weight reduction). At adulthood, males (both cftr$^{-/-}$ and controls) are more sensitive to CB_1 receptor activation compared to females of both strains.

CANNABINOID SIGNALING IN HUMAN BRONCHIAL EPITHELIAL CELLS

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Cannabinoid receptors (CBR) are coupled to $G_{i/o}$ –proteins, among others inhibiting cAMP production, modulating ion channels and stimulating MAP kinase pathways. Cannabinoids, both exogenous (Δ^9THC) and endogenous (anandamide and virodhamine) compounds possess immunomodulatory properties. They may be involved in airways pathophysiology by modulating the ratio of pro- and anti-inflammatory mediators released by airway epithelial cells. Ca^{2+} -entry has been implicated in these processes. We investigated CBR subtype expression and the effects of the endogenous cannabinoid, virodhamine (VIR), on $[Ca^{2+}]_i$, cAMP accumulation and arachidonic acid (AA) in/by human bronchial epithelial cells (16HBE14o$^-$)
We found both CB_1R and CB_2R mRNA expression in 16HBE14o$^-$. VIR decreased concentration-dependently forskolin-induced cAMP production, which was PTX-sensitive and mediated by CB_2Rs. VIR concentration-dependently released Ca^{2+} from internal stores (maximally 57.1 ± 7.0 nM) and induced capacitative Ca^{2+}-entry (maximally 97.2 ± 24.6 nM). Higher virodhamine concentrations (>10μM) induced, after some delay, non-capacitative Ca^{2+}-entry, which was inhibited fully by the channel inhibitors Gd^{3+} and La^{3+} and partly by the TRPV channel inhibitors capsazepine (TRPV1 inhibitor), ruthenium red (TRPV1 & TRPV4 inhibitor).

VIR increased concentration-dependently AA release (maximally by 2-fold), which in turn was found to mediate non-capacitative Ca^{2+} -entry.
Our results indicate that cannabinoids are able to activate various signaling systems in bronchial epithelial cells, potentially affecting pro- and anti-inflammatory mediator release.

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INCREASE IN TOTAL DELTA-THC IN NEDERWIET AS SOLD IN DUTCH COFFEE SHOPS

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Δ^9-Tetrahydrocannabinol (THC) is the main psycho-active compound in marihuana and hashish. The aim of this study was to investigate the concentration of THC in marihuana and hash as sold in Dutch coffeeshops. In addition we wanted to know whether there are differences between the cannabis products originating from Dutch grown hemp (nederwiet) and those derived from imported hemp. Therefore, the total concentration of THC has been monitored in cannabis preparations sold in Dutch coffee shops since 1999. This yearly monitoring was issued by the Ministry of Health after reports of increased potency. The level of the main psychoactive compound, Δ9-tetrahydrocannabinol (THC), is measured in marijuana and hashish. A comparison is made between imported and Dutch preparations, and between seasons. Samples of cannabis preparations from randomly selected coffee shops were analysed using gas chromatography (GC-FID) for THC, CBD and CBN. In 2005, the average THC level of Dutch home-grown marijuana (Nederwiet) (17,7.3% THC) was significantly higher than that of imported marijuana (6,7% THC). Hashish derived from Dutch marijuana (Nederhasj) contained 26,0 % THC in 2005, compared with 16,9% THC in imported hashish. The average THC percentage of Dutch marijuana, Dutch hashish and imported hashish was significantly increased since the start of the study in 1999. During the study period, the THC percentage in imported marijuana remained unchanged at about 6%. Whether the increase in THC levels causes increased health risks for users can only be concluded when more data are available on adjusted patterns of use, abuse liability, bioavailability and levels of THC in the brain.

HOW CANNABIS INDUCES SCHIZOPHRENIA. AN INTEGRATIVE HYPOTHESIS FROM THE NEUROBIOLOGICAL LITERATURE.

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Epidemiological studies and reanalyses of existing data have shown that adolescent cannabis users have a higher risk of developing psychosis and schizophrenia than their non-using peers. Recent technological developments in human laboratory and animal model research of brain function have provided new insights on the adolescent brain. From these studies it became clear that the prefrontal cortex and mesocortical projections still undergo major changes during adolescence.
In vivo and in vitro research with cannabinoids has unraveled some of the mechanisms by which cannabinoids affect the central nervous system. It has been found that endogenous cannabinoids play an important role in the regulation of apoptosis one of the most important mechanisms in brain development.
We have reviewed recent scientific literature on the biological mechanisms underlying psychosis and schizophrenia and the neurobiological targets of THC, the main psychoactive compound in cannabis.We have combined the results of these neurodevelopmental, neurochemical and neurobiological studies. This illustrates how cannabis use during adolescence permanently affects the brain and consequently leads to psychosis or schizophrenia. The findings from these studies will be summarized and integrated into a general hypothesis for the neurobiological mechanism of schizophrenia, in particular schizophrenia induced by cannabis use during adolescence. The hypothesis illucidates the following questions:

- Why are adolescent brains more vulnerable to the effects of cannabis than adult brains?
- Which developmental processes occur in the adolescent brain that makes them more vulnerable to the effects of cannabis?
- In which way affects cannabis these developmental processes?

EFFECTS OF CANNABIS AND DELTA-9-TETRAHYDROCANNABINOL ON RESPONSE PRIMING IN HUMANS

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The Simon effect refers to the finding of faster responses in case a stimulus and response position correspond than when they do not. Dual route models propose that spatial stimulus features prime the corresponding response via a direct route, whereas response selection occurs via an indirect route. The Simon effects depends on the correspondence condition of the predecessor, that is, the Simon effect is absent after a noncorresponding predecessor, it only shows up after a corresponding predecessor. We account for this finding by executive control over direct route priming achieved by dorsolateral prefrontal cortex (DLPFC) functioning.

Recent studies showed an increase of spatial conflicts by Cannabis. For example, the execution of antisaccades and spatial working memory was hampered indicating the involvement of DLPFC. Therefore, we investigated whether Cannabis interferes with executive control over reponse priming.

A double-blind study was run with 24 healthy adults getting delta-9-THC, Cannabis or a placebo. By EEG event-related brain potentials were recorded in the Simon task, and the lateralized readiness potential (LRP) was calculated as an indicator of specific hand activation. Usually, in noncorresponding conditions there is an early incorrect activation in the LRP replaced by correct response hand activation later on. This early LRP lateralization is seen to reflect response conflict and does not occur after a noncorresponding predecessor.

In line with our assumption a Simon effect after a noncorresponding predecessor was present with medication affecting also the early LRP lateralization. Moreover, delta-9-THC and Cannabis enlarged early attention related ERP components but reduced the later P300.

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PRODUCTION OF MORE SOLUBLE CANNABINOIDS BY BACTERIAL BIOTRANSFORMATION

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Many pharmacological effects are attributed to cannabinoids and in particular δ 9-THC. Their hydrophobicity and consequent poor solubility of this family of compounds in water is an obstacle for their pharmacological use; the cannabinoids tend to partition into fat tisues, causing their rapid elimination from blood circulation.

To produce more soluble metabolites, microbial biotransformation of δ 9-tetrahydrocannabinoids (δ 9-THC) was investigated using different bacterial strains. A screening program was conducted on 196 strains from the Enzyscreen collection complemented with 15 strains isolated from an oil polluted soil sample. 61 out of 211 strains showed activities, all leading to the production of more polar compounds. Larger scale production with some strains was done and the metabolites were isolated on a 1-10 mg scale, purified, and their structure were elucidated by use of LC-Mass and ^{1}H-NMR. The structures of the metabolites formed will be presented.

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Program and Abstracts

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