CANNABIN🍁ID conference 2017

IACM 9th Conference on Cannabinoids in Medicine

29-30 September 2017
Cologne, Germany

PROGRAM AND ABSTRACTS

Place Maritim Hotel
Heumarkt 20
50667 Cologne
Germany

Registration Fee The registration fee is 350 Euros. Students pay a reduced fee of 150 Euros. The registration fees include daily rates (lunch for all days, coffee during the breaks) and an evening dinner on Saturday.

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Mark Ware
Roger Pertwee

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GENERAL INFORMATION

Simultaneous translation

There will be simultaneous translation from english into german.

Badges

Please wear your badge at all times during the conference. You will also need to wear it for the evening dinner.

Dinner of IACM partner organizations and ambassadors

On Friday we will have a dinner with the IACM partner organizations and ambassadors.

Conference Dinner

On Saturday evening we will have our gala dinner at the conference place.

IACM Awards

During the conference dinner the IACM will honour six people for their major contributions to cannabinoid research and/or to the re-introduction of cannabis into modern medicine with the IACM Award.

IACM General Meeting

The IACM will hold its general meeting on Saturday afternoon.

Poster Sessions

There will be two poster sessions at the conference:

Session 1: Friday 13:00 – 15:00 during and after the lunch break.

Session 2: Saturday, 12:55 – 15:00 during and after the lunch break.

All posters will be available until the end of Poster Session 2 on Saturday. Presenters of posters with even numbers will be present at Poster Session 1, presenters of posters with odd numbers will be present at Poster Session 2.

Friday, September 29

8:45   Opening

Where do we stand?

9:00-12:30   Session 1: Accepted medical uses and medications
Chairs: Mark Ware & Donald Abrams

9:00-9:35   Donald Abrams (USA)
Cannabis-based medicines: an introductory overview of all the major clinically relevant known knowns and known unknowns

9:35-10:10   Ryan Vandrey (USA)
Evaluating the impact of cannabis use in the human laboratory and via patient registry surveys

10:10-10:45 Kirsten Müller-Vahl (Germany)
Current cannabis-based medicines: a clinician's perspective

10:45-11:15 Coffee Break

11:15-11:30 Timna Naftali (Israel)
The effect of cannabis on Crohn's disease patients

11:30-11:45 Lihi Bar-Lev Schleider (Israel)
Epidemiological characteristics, safety and efficacy of medical cannabis use in cancer patients

11:45-12:00 Aleksi Hupli (Finnland)
Medical cannabis for ADHD: a medical sociological patient case study of cannabinoid therapeutics in Finland

12:00-12:15 Carl Roberts (UK)
Exploring the munchies: investigation of cannabis effects on human appetite and the development of the cannabis eating experience questionnaire

12:15-12:30 Ran Abuhasira (Israel)
Epidemiological characteristics, safety and efficacy of medical cannabis in older subjects

12:30-13:00   **Questions from a panel of experts**
What information do patients and their clinicians need?

13:00-15:00   **Lunch and poster session I**

15:00-16:20   **Session II: Genetics, strains and quality**
Chairs: Ethan Russo & Jahan Marcu

15:00-15:35   **Ethan Russo** (USA)
Chemovars (and a comparison of sativa & indica)

15:35-16:10   **Jahan Marcu** (USA)
Nature, variability & safety of marketed cannabis (NB pesticides) & how to optimize the safety & medical efficacy of marketed cannabis

16:10-16:35   **Break**

16:35-18:35   **Session III: Laws and politics**
Chairs: Kirsten Müller-Vahl & Ilya Reznik

16:35-17:05   **Mark Ware** (Canada)
Impact of new regulations on medical and recreational cannabis

17:05-17:20   **Jeffrey Hergenrather** (USA)
Country report: USA

17:20-17:35   **Ilya Reznik** (Israel)
Country report: Israel

17:35-17:50   **Franjo Grotenhermen** (Germany)
Country report: Germany

17:50-18:05   **Sébastien Béguerie** (France)
 Country report: France

18:05-18:35   **Questions from a panel of experts**
What are the best (and worst) ways forward for patients and their clinicians?

19:00-22:00   **Dinner of IACM partner organizations and ambassadors**

Saturday, September 30

Where do we go?

9:00-12:55	**Session IV: Emerging new indications**
	Chairs: Roger Pertwee & Guillermo Velasco

9:00-9:35   **Jonathan Page** (USA)
Biochemical genomics of cannabis strain diversity

9:35-10:10   **Roger Pertwee** (UK)
Future exploitation in the clinic of the endocannabinoid system and of synthetic drugs - most promising future directions

10:10-10:45   **Guillermo Velasco** (Spain)
Promising future directions: cannabinoid medicines versus cancer

10:45-11:15   **Coffee Break**

11:15-11:30   **Yosef Sarne** (Israel)
Reversal of age-associated cognitive impairments by ultra-low doses of tetrahydrocannabinol

11:30-11:45   **Elon Eisenberg** (Israel)
Cannabis treatment in hospitalized patients, using the syqe -exo inhaler - results of a pilot open-label study

11:45-12:00   **Zoltán Balogh** (Hungary)
Endocannabinoid interactions in the regulation of behavioral responses to trauma

12:00-12:15   **Jan G. Ramaekers** (Netherlands)
Brain kinetics of neurometabolites during cannabis intoxication

12:15-12:50   **Daniele Piomelli** (USA)

The future of cannabis-based medicines: a pharmacologist's perspective

12:50-15:00   **Lunch and poster session II**

15:00-17:00	**Session V: Knowledge and education**

Chairs: Raquel Peraube & Franjo Grotenhermen

15:00-15:40   **Franjo Grotenhermen** (Germany)

Promising indications with limited clinical evidence

15:40-16:20   **Raquel Peyraube** (Uruguay)

What questions do clinicians and patients have on a treatment with cannabis-based medicines?

16:20-17:00   **Questions from a panel of experts**

What should clinicians, patients and regulators know? What questions are still waiting for an answer?

17:00-17:15   **Break**

17:15-18:00	**IACM General Meeting**

19:00-22:00   **Dinner with Award Ceremony**

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Oral Presentations

CANNABIS-BASED MEDICINES: AN INTRODUCTORY OVERVIEW OF ALL THE MAJOR CLINICALLY RELEVANT KNOWN KNOWNS AND KNOWN UNKNOWNS

Donald I. Abrams, MD

University of California San Francisco, San Francisco, CA USA

In anticipation of more states voting to approve medicinal and recreational cannabis in the November 2016 election, the National Academies of Sciences, Engineering and Medicine (NASEM) was commissioned by a number of US federal and state agencies to conduct a rapid turn-around comprehensive review of the recent medical literature. A 16-member committee of diverse individuals was tasked with reviewing information published since the Institute of Medicine report on the topic released in 1999. The committee met between June 2016 and December 2016 with the final report- **Health Effects of Cannabis and Cannabinoids**- issued in January 2017. The committee adopted the key features of a systematic review process, conducting an extensive search of relevant databases (e.g., Medline, Embase, the Cochrane Database of Systematic Reviews, PsycINFO). The initial search resulted in more than 24, 000 articles, of which the committee considered more than 10,000 abstracts to determine their relevance for the report. Primacy was given to recently published systematic reviews and high-quality primary research that studied one or more of the committee's 11 prioritized health endpoints. These included therapeutic effects; cancer incidence; cardiometabolic risk; respiratory disease; immune function; injury and death; prenatal, perinatal and postnatal outcomes; psychosocial outcomes; mental health; problem cannabis use; and cannabis use and abuse of other substances. Informed by the reports of previous IOM committees, the committee developed standard language to categorize the weight of evidence regarding whether cannabis or cannabinoids use (for therapeutic purposes) are an effective or ineffective treatment for the prioritized health endpoints of interest. The 5 levels of evidence assigned were conclusive; substantial; moderate; limited; and no or insufficient. In the Therapeutics chapter, the report concluded that there was conclusive or substantial evidence that cannabis or cannabinoids are effective for the treatment of pain in adults; chemotherapy-induced nausea and vomiting (oral cannabinoids) and spasticity associated with multiple sclerosis (oral cannabinoids). Moderate evidence was found for sleep disturbances associated with a number of medical disorders. The evidence supporting improvement in appetite, Tourette syndrome, anxiety and posttraumatic stress disorder was described as limited. In the literature published through August 2016, the committee found no or insufficient evidence to support or refute the conclusion that cannabis or cannabinoids are effective for treatment of cancer, irritable bowel syndrome, epilepsy and a variety of neurodegenerative disorders including Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis. A chapter of the NASEM report was devoted to enumerating the multiple barriers to conducting research on cannabis in the US that helps to explain the paucity of positive therapeutic benefits in the published literature to date.

COMPARATIVE PHARMACODYNAMIC INVESTIGATION OF ORAL, SMOKED, AND VAPORIZED CANNABIS

Ryan Vandrey,[1] Nicolas J. Schlienz[1], Evan S. Herrmann[2], George E. Bigelow[1],
John M. Mitchell[3], Ron Flegel[4], Charles LoDico[4], Edward J. Cone[1]

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Background: In the U.S., a burgeoning cannabis marketplace exists that offers a growing number of consumable cannabis goods and products intended for use via a variety of methods of administration. Few controlled studies that have been conducted using administration methods other than smoking. We conducted a series of studies to directly compare the dose effects of cannabis following oral, smoked, and vaporized routes of administration.
Methods: The comparative pharmacokinetic and pharmacodynamic effects of cannabis were assessed in healthy adults at 0, 10mg, and 25mg THC dose across routes of administration. 17 participants completed all doses within each route. Participants had a history of cannabis use, but had not used cannabis for at least one month prior to randomization. Outpatient sessions were conducted 1 week apart. Pharmacokinetic and pharmacodynamics assessments were obtained at baseline and for 8 hours following drug exposure. Analyses compared active dose conditions with placebo, and the same doses were compared across routes of administration. Correlations between behavioral measures and cannabinoids in blood and oral fluid were evaluated.
Results: Dose dependent drug effect ratings, cardiovascular effects, and cognitive performance effects were observed across routes of administration. Peak drug effects occurred within fifteen minutes for inhaled cannabis followed by a gradual return to baseline. In contrast, oral cannabis drug effects onset +60-90min post-administration and remained at peak levels for a longer period of time. Cardiovascular and cognitive performance effects had a different time course with cardiovascular effects occurring more immediately (peak effect at +90min) compared with subjective drug effects (peak effect at +180min) and cognitive performance impairment (peak effect at +300min). The magnitude of peak drug effects was comparable across the smoked and oral routes of administration, but greater following vaporized cannabis administration. Blood cannabinoid levels were significantly correlated with subjective drug effect ratings and inversely correlated with some performance tasks. Oral fluid THC was significantly correlated with self-reported Drug Effect following smoked (r = 0.21) and vaporized (r = 0.26) cannabis, but not oral cannabis. Oral fluid THC was not significantly correlated with psychomotor, divided attention, or working memory performance following any route of administration.
Conclusion: Significant variability in the pharmacodynamic effects of cannabis was observed across doses and as a function of route of administration. At the same doses, the magnitude of peak drug effects was comparable for both oral and smoked, but higher for vaporization, suggesting it is a more efficient route of cannabis delivery. Blood cannabinoids were better biomarkers of acute drug effects than oral fluid cannabinoids, but neither was consistently well correlated with performance on cognitive tasks.

CURRENT CANNABIS-BASED MEDICINES: A CLINICIAN'S PERSPECTIVE

Kirsten R. Müller-Vahl

Department of Psychiatry, Socialpsychiatry and Psychotherapy, Hannover Medical School

The kind and number of cannabis-based medicines (CBMs) is constantly increasing. Availability for patients differs from country to country and strongly depends on accessibility and costs. At present time, medicinal cannabis standardized for delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) is available in many countries. Contents of cannabinoids differ from 1-24% (for THC) and <0.5-9% (for CBD). Different routes of intake can be used including smoking, vaporizing, and oral intake. In addition, in many countries cannabis extracts can be prescribed such as nabiximols standardized for TCH and CBD at a 1:1 ratio administered as an oral spray. Finally, pure THC (dronabinol), pure CBD and synthetic THC products such as nabilone can be used.

Due to a tremendous lack of well-designed clinical trials, for most indications it is unknown which CBM is most effective. Therefore, clinicians and their patients should use a pragmatic approach, when treatment with CBM shall be initiated. Firstly, it has to be found out whether CBMs in general are effective and well-tolerated. Secondly, – if available and possible – the most effective CBM has to be identified: pure THC, a cannabis extract, or the whole plant. Thirdly, the most effective and safe route of administration has to be identified in the particular patient. Finally, the optimal dose and number of intakes per day have to be defined. Thus, in most patients, very soon it becomes clear, whether or not CBM are an effective and well-tolerated kind of treatment that is superior to well-established treatment strategies. However, very often it takes some time to adjust individual treatment.

For clinicians it is important to acknowledge patients' preferences in particular in terms of the route of intake. While some patients prefer inhalation, others prefer oral intake. Preferred route of intake also depends on the particular indication. In some patients a combination of different routes of intake and even different CBMs is most effective. Clinicians should inform their patients about different available CBMs describing both advantages and disadvantages. Whenever possible, inhalation using a vaporizer should be preferred over smoking.

For the future, it would be very useful to simplify this time consuming and difficult procedure. For example it would be helpful, if patients could easily try different CBMs containing different amounts of THC and CBD to identify the most effective ratio. At present time, other cannabinoids and non-cannabinoid ingredients are largely ignored, since it is unknown whether efficacy and safety also depends on these substances. There is evidence that substances such as palmitoylethanolamide (PEA) enhance the action of anandamide through an increase in the affinity for receptors and/or a decrease in enzymatic degradation achieving a so called "entourage effect" and enhance beneficial effects of CBMs. A broader spectrum for administration including retard formulations would further extend the treatment options for CBMs. Finally, there is preliminary evidence that cannabinoid modulators such as inhibitors of the catabolic enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MGLL), respectively, that regulate levels of anandamide (AEA) and 2-arachidonoylglycerol (2-AG) may be sophisticated new treatment strategies.

The identification of "endocannabinoid deficiency syndromes" would be very helpful to define conditions that can be improved or even cured by substances with agonistic effects on the endocannabinoid system.

THE EFFECT OF CANNABIS ON CROHN'S DISEASE PATIENTS

Naftali Timna MD[1,2], Lihi Bar Lev Schlieder MA[3], Fred Meir Konikoff MD, PhD[1,2]

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Introduction: We aimed to assess the effect of cannabis on Crohn's disease patients.

Methods: In a double blind, randomized placebo-controlled trial patients received either cannabis oil 15% CBD and 4% THC or placebo for eight weeks. Parameters of disease including Crohn's disease activity index (CDAI), inflammatory markers and quality of life (QOL) were assessed before, during and after treatment.

Results: The cannabis group had 18 patients (13 males) and the placebo group had 21 patients (9 males), with an average age of 35.1 ±12.7. In the cannabis group, the CDAI score improved from 279.3 ±72.9 before the treatment to 118.6 ±71.5 after eight weeks of cannabis treatment ($p < 0.001$), whereas in the placebo group the score changed from 291.2 ±111.1 to 212.6 ±102.4 ($p < 0.05$). Quality of life score in the cannabis group improved from 74.8 ±20.0 to 96.3 ±17.6 ($p < 0.001$). In the placebo group, quality of life was 71.6 ±13.7 before and 79.9 ±16.2 after treatment ($p < 0.05$).

Conclusions: This eight weeks trial shows that cannabis has a positive effect on the quality of life and on the CDAI of Crohn's disease patients. In light of these findings, cannabis should be further explored as a possible therapy alongside conventional modalities. Larger and longer follow up trials should be conducted.

EPIDEMIOLOGICAL CHARACTERISTICS, SAFETY AND EFFICACY OF MEDICAL CANNABIS USE IN CANCER PATIENTS

Lihi Bar-Lev Schleider MA[1,2], Raphael Mechoulam PhD[3], Victor Novack MD PhD[1]

[1] Clinical Research Center, Soroka University Medical Center and Faculty of Health Sciences, Ben-Gurion University of the Negev, Be'er-Sheva, Israel. [2] Research Department, Tikun Olam LTD. Israel. [3] School of Pharmacy, the Hebrew University of Jerusalem, Israel.

Background: Cancer is a major public health problem as the leading cause of death among Americans. Palliative treatment aimed to alleviate pain and nausea in patients with advanced disease is a cornerstone of oncology. In 2007, Israeli Ministry of Health began providing approvals for medical cannabis, mainly for the palliation of the cancer symptoms. The aim of this study is to characterize the epidemiology of cancer patients receiving medical cannabis treatment and describe safety and efficacy of this therapy.

Methods: We analyzed the data routinely collected as part of the treatment program on 2,730 medical cannabis cancer patients registered in Tikun-Olam (TO) during two years.

Results: The cancer patients represented 60% of the population receiving license for medical cannabis. The average age was 59.9±16.5 years, 54.3% women and 21.5% of the patients reported previous experience with cannabis. The most frequent types of cancer were: breast (16.7%), lung (13.6%), pancreatic (8.3%) and colorectal (8.1%) with 51.2% being at stage 4. The main symptoms requiring therapy were: pain (76.0%, median intensity 7/10), sleep problems (72.9%), weakness (66.6%), nausea (53.3%) and lack of appetite (48.8%). After six months of follow up, 688 patients (25.2%) died and 243 (8.9%) stopped the treatment. Of the remaining, 832 (46.2%) responded; 95.8% reported an improvement in their condition, 30 patients (3.6%) reported no change and four patients (0.4%) reported deterioration in their medical condition.

Conclusions: Cannabis as a palliative treatment for cancer patients seems to be well tolerated, effective and safe option to help patients cope with the malignancy related symptoms.

MEDICAL CANNABIS FOR ADHD: A MEDICAL SOCIOLOGICAL PATIENT CASE STUDY OF CANNABINOID THERAPEUTICS IN FINLAND

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[2] IACM Patient Representative, Finland

There are numerous qualitative and quantitative studies reporting a strong association between Attention Deficit/Hyperactivity Disorder (ADHD) and cannabis use (e.g. *Loflin et al., 2014, Subst. Use Misuse 49, 427–434; Bidwell et al., 2014, Drug Alcohol Depend. 135, 88–94*), including a recent online study (*Mitchell et al., 2016 PLoS ONE 11(5): e0156614. doi:10.1371/journal.pone.0156614*). Many of the studies, however, often interpret cannabis use automatically, and often misleadingly, as *drug abuse*, (e.g. *Ramtekkar & Mezzacappa, 2013, Comprehensive Psychiatry, 54, e14*) not as a potential, albeit often illegal, form of (self-) medication. Medical cannabis patients in general are using cannabinoid therapeutics to substitute alcohol, illicit drugs and commonly used prescription drugs for better symptom management and for experiencing fewer side-effects (*Lucas et al., 2016 Drug and Alcohol Review, 35, 326– 333; Reiman, 2009, Harm Reduction Journal, 6:35*). Like with any other type of medication, potential harms and the risk of developing a substance abuse disorder should be also taken into account, especially for this patient group (*Notzon et al., 2016, Journal of Attention Disorders, 1-6*), although moderate use of cannabis can also help to retain individuals with ADHD from other, more harmful substances, like cocaine (*Aharonovich et al., 2006, The American Journal of Drug and Alcohol Abuse, 32:4, 629-635*).

Methods: This paper offers a detailed medical sociological case study of a contemporary cannabinoid therapeutics (CT) patient in Finland. The patient is a 45- year old male who was diagnosed in adulthood with Hyperkinetic disorder (ICD-10 definition), more commonly known as Attention Deficit Hyperactivity Disorder (ADHD, according to DSM-V), combined type. Since 2010 he has had legal medical prescriptions to the whole plant CT products Bedrocan ® and Bediol ®, produced in the Netherlands. The patient, who is a EU-citizen living in Finland since 1995, received the primary prescription for CT from a physician in Germany, and the prescriptions were later confirmed by a Finnish neurologist. The patient searched CT after experiencing adverse effects from more commonly used psychopharmaceutical treatments for ADHD, namely central nervous system stimulant (CNS) methylphenidate (Ritalin ®). In addition to providing a detailed case study, this presentation also aims to provide a brief non-systematic literature review of recent studies involving the use cannabinoids in alleviating some of the primary physiological and psychological symptoms of ADHD. At the end of this presentation we will also provide a short overview of the use of cannabinoid therapeutics in Finland and evaluate possible barriers for a successful cannabinoid therapy. **Results:** According to the patient, Bedrocan is especially helpful for the symptoms of ADHD. Another CT product, Bediol ®, which has relatively high cannabidiol (CBD) levels, was also found to be helpful to balance some of the dronabinol effects of Bedrocan ®, as well as having other medical benefits. The monetary cost of the medication, the lack of governmental reimbursement from the Finnish government and insufficient training of medical professional about CT remains to be barriers for a successful CT in Finland.

Conclusion: A detailed case study, although not generalizable, can bring important insights to further develop clinical practice and research around cannabinoid therapeutics. Through our case study and review of the literature, we found there is enough evidence to show that especially for individuals who do not find relief for their symptoms from CNS stimulants and/or experience adverse effects, cannabinoid therapeutics can offer a safe and efficient mode of treatment, possibly in conjunction with CNS stimulants, and other forms of therapy. Further studies are however needed to see what are the most efficient modes and dosages of administration, and what kind of cannabinoid and terpenoid combinations are ideal for what kind of sub-types of ADHD. Investigation of the general attitudes and knowledge of physicians about cannabinoid therapeutics in Finland is also warranted.

EXPLORING THE MUNCHIES: INVESTIGATION OF CANNABIS EFFECTS ON HUMAN APPETITE AND THE DEVELOPMENT OF THE CANNABIS EATING EXPERIENCE QUESTIONNAIRE (CEEQ).

Carl Roberts.[1], Gerry Jager[2], Paul Christiansen[1], & Tim Kirkham[1]

[1]Department of Psychological Sciences, University of Liverpool, UK, [2] Wageningen University and Research Centre, Wageningen, 6708 PB, Netherlands

Introduction: It is understood, from anecdotal evidence, that cannabis intoxication leads to increased, often voracious, appetite and enhanced appreciation of food; a phenomenon colloquially referred to as the "munchies". This action appears to reflect actions of the drug on brain systems involved in the normal regulation of appetite.
Despite centuries of cannabis use, and an advanced behavioural pharmacology literature, most of our knowledge about the drug's actions on the psychological and behavioural aspects of appetite in people remains largely anecdotal in nature. There is little empirical evidence to substantiate users' claims, and human lab studies have focused principally on food intake measures, rather than the psychological factors which affect eating. This study addresses the shortfall in the scientific literature, by characterising the nature of "the munchies" in terms of alterations to motivation to eat, modulation of appetite, sensory reward, food intake and changes in food preferences.
Method: We devised a Cannabis Eating Experience Questionnaire, (hosted online) which asked participants various questions about their cannabis use, BMI, and demographic information, as well as a 46 likert response item scale which asked specifically about eating behaviour under the influence of cannabis (the munchies). We used exploratory and confirmatory factor analysis (on an English speaking sample of 591 and a Dutch speaking sample of 167 participants) to develop a reliable scale for assessing cannabis effects on the motivational factors that drive food seeking behaviour.
Results: Our 'munchies' scale identified 3 subscales from exploratory factor analysis; items that related to hedonic eating, motivation to eat and termination of eating. Each scale had a high test-retest reliability (0.88, 0.92 and 0.75 respectively) and the resulting factor structure was confirmed in a separate, Dutch speaking sample, suggesting cross cultural validity. Regression analysis suggested that motivation to eat appeared reduced with increased frequency of use. Importantly many other responses on the questionnaire relate to several aspects of 'the munchies' that are not previously reported elsewhere in the literature.
Conclusions: The phenomenon of 'the munchies' is much more complicated than previous research suggests. The majority of respondents across samples do report an enhancement of the eating experience, although this is not entirely uniform and does not pertain simply to sweet foods. Our data suggest that all foods become more appealing, including many healthy foods. This is in line with the view that the (endo)cannabinoids can enable sophisticated fine tuning of palatability (for all food types) via central and peripheral mechanisms – a finding that is salient in the context of using CB1 receptor agonists in clinical settings to help halt the progression of wasting diseases associated with cancer and AIDS.

EPIDEMIOLOGICAL CHARACTERISTICS, SAFETY AND EFFICACY OF MEDICAL CANNABIS IN OLDER SUBJECTS

Ran Abuhasira B. Med.Sc [1], Lihi Bar-Lev Schleider MA[1,2], Victor Novack MD PhD[1]

[1] Clinical Research Center, Soroka University Medical Center and Faculty of Health Sciences, Ben-Gurion University of the Negev, Be'er-Sheva 84101, Israel.
[2] Research Department, Tikun Olam LTD.

Introduction: In 2007, Israeli Ministry of Health began providing registrations for medical cannabis. Today there are ~30,000 medical cannabis patients in Israel; more than 25% receive treatment at Tikun-Olam (TO). A large part of this population is elderly people in whom the efficacy and safety of the cannabis treatment is not fully elucidated. The aim of this study is to characterize the patient population aged 65 and above receiving medical cannabis treatment.
Methods: We analyzed the data routinely collected as part of the treatment program on 1,946 medical cannabis patients aged 65 and above registered in TO during 2015-2017.
Results: Patients above 65 years of age represented 37.3% out of the whole population. The most frequent indications were: cancer (64.6%), nonspecific pain (25.9%), Parkinson's disease (PD) (4.8%), post-traumatic stress disorder (PTSD) (0.7%), inflammatory bowel disease (0.5%) and others (3.5%). The average age was 75.8±7.5 years, 46.6% were males. 17.5% of the patients reported previous experience with cannabis. The main symptoms requiring therapy were: pain (83.1%, median intensity 8/10), sleep disturbances (71.2%), weakness (57.6%), anxiety and depression (57.0%), digestion problems (36.1%). After six months of follow up, 249 patients (12.8%) died and 165 (8.5%) stopped the treatment. Of the remaining, 596 (45.7%) responded; 523 patients (87.7%) reported an improvement in their condition, 67 patients (11.2%) reported no change and six patients (1.0%) reported deterioration in their medical condition.
Conclusions: This is the largest study describing the characteristics of the medical cannabis in older subjects in Israel. The treatment appears to be safe and efficacious in this population. Establishing a national clinical investigation program to elucidate the safety and efficacy of the therapy in the elderly is imperative.

CANNABIS CHEMOVARS

Ethan Russo[1], Mark Lewis[2], Kevin Smith[2]

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[2]NaPro Research

An advanced Mendelian cannabis breeding program has been developed utilizing biochemical markers to maximize the yield of phytocannabinoids and terpenoids with the aim to improve therapeutic efficacy and safety. Cannabis is often divided into several categories based on cannabinoid content. Type I, THC-predominant, is the prevalent offering in both medical and recreational marketplaces. In recent years, the therapeutic benefits of cannabidiol (CBD) have been better recognized, leading to the promotion of additional chemovars: Type II cannabis that contains both THC and CBD, and CBD-predominant Type III cannabis. While high-THC and high-myrcene chemovars dominate markets, these may not be optimal for patients who require distinct chemical profiles to achieve symptomatic relief. Type II cannabis chemovars that display CBD- and terpenoid-rich profiles have the potential to improve both efficacy and minimize adverse events associated with THC exposure. Cannabis samples were analyzed for cannabinoid and terpenoid content, and analytical results are presented via PhytoFacts, a patented method of graphically displaying phytocannabinoid and terpenoid content, as well as scent, taste and subjective therapeutic effect data: https://phytofacts.info . Examples from the breeding program are highlighted, and include Type I, II and III cannabis chemovars, those highly potent in terpenoids in general, or single components: limonene, pinene, or linalool, for example. Additionally, it is demonstrated how Type I-III chemovars have been developed with conserved terpenoid proportions. Specific chemovars may produce enhanced analgesia, anti-inflammatory, anti-convulsant, antidepressant and anti-anxiety effects, while simultaneously reducing sequelae of THC such as panic, toxic psychosis, and short-term memory impairment.

IMPACT OF NEW REGULATIONS ON MEDICAL AND RECREATIONAL CANNABIS

Mark Ware

McGill University, Montreal, Quebec, Canada

Regulations around medical and nonmedical use of cannabis are under serious discussion and development in many countries around the world. This presentation will review the current status in Canada around the recent (Dec 2016) Task Force report on the legalization and regulation of cannabis, and the subsequent discussions at the federal and provincial levels regarding the implementation of the proposed new Cannabis Act. With this legislation, Canada will become only the second country worldwide to move ahead with legalization of cannabis for nonmedical purposes. The lessons that are being learned in Canada maybe of interest to other countries considering similar legislation. This presentation will also consider some of the opportunities that changing policy will provide in terms of research and education around cannabis.

COUNTRY REPORT: U.S.A

Jeffrey Hergenrather

Cannabis physician in California

With incarceration of more than 2.4 million Americans, approximately half for drug related offenses, the public around the nation has taken the initiative to change laws pertaining to cannabis use. Now the majority of states have provided for at least the medical use of marijuana despite the federal prohibition. Federal law changes are proposed with bipartisan support but lie fallow in committees without sufficient votes for passage. Public perception of cannabis is changing by word of mouth, in part from the influence of progressive journalists, TV personalities, and financial and commercial interests. With the changes in public perception so are the population demographics changing in patients consulting for cannabis recommendations. Many cannabis naïve older adults and parents of children are looking to cannabis where traditional medicines have failed. Finally, the bias against cannabis persists with headlines, misinformation, and misdirected research promoting assertions of harm from cannabis use despite evidence exonerating cannabis from those assertions.

MEDICINAL CANNABIS IN ISRAEL:
CURRENT STATUS AND FUTHER DIRECTIONS

Ilya Reznik[1,2]

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Cannabis as an ethical and viable treatment modality has been debated for decades. In recent years, a marijuana/cannabis and its' products was reintroduced and became a legitimate treatment in several countries under the label of Medicinal Cannabis (MC). Now, the National MC program in Israel has the largest number of patients *(per capita)* population in the world. Also, Israel is still the marijuana research capital of the world, mostly due to the renowned works of the grandfather of the marijuana research Prof. Raphael Mechoulam (Hebrew University, Jerusalem) and the large group of his fellows and collaborators.

As soon as the Dangerous Drugs Ordinance Act (1973) and the Regulations made under this ordinance, as well as the provisions of the Single Convention on Narcotic Drugs define the cannabis as a "dangerous" substance, "that is not medicine and should be strictly controlled", several years ago the Israeli Ministry of Health (MoH) established a "government agency" (IMCA) pursuant to the provisions of the said Convention. Since 1995 Israel has issued approximately 39,000 licenses (~29,000 active/valid today) for MC (the actual demand of licensure is estimating ~ 300.000 potential permanent MC patients);

Under current, mostly non-efficient regulation, IMCA (after non-transparent review made by anonymous clerks) may approve (or reject) a specialist physician's recommendation for providing MC for specific patients. Nevertheless, the number of licensed patients in Israeli has risen dramatically in the last few years, despite of the very limited list of the formal indication for MC approvals and very strict criteria for proposed patient's selections, which has been made by the MC Authority. The rapid growth of licensed patients accompanied by the continuing resistance of formal medical establishment (incl. Israel Medical Associations and its professional Societies, such as Pain Specialists, Family Physicians, Addiction Medicine etc.). In this atmosphere, the small group of clinicians has become a responsible for vast majority of the cannabis-treated patients.

Most recently, Israeli MoH initiated the major reform in the field of MC, directing for "medicalization" of cannabis products, which may "outline is to ensure on the one hand an appropriate indication for patients, access to care and supply of good quality cannabis products, and on the other hand appropriate oversight of a product that is defined as a "dangerous drug".In the scope of this reform, the IMCA announced that medical cannabis will be available in pharmacies in Israel, and that more doctors would be allowed to prescribe it. The first (in the history of the world!) Certification Course under the government auspice for the physicians attested and qualified them for the direct prescription of the MC (in forms of GMP product) as a regular medicine. So, nowadays the situation with MC in Israel could be described as transitional, as soon as the new regulations are being made by the. We still have a lot to do: to improve relationships with patients organizations and general public, and with suppliers/growers; to organize systematic learning and training for health care practitioners etc. I hope that the recent clinical and scientific advances and our success with the cannabis-treated patients will attract more physicians and other health care practitioners to be involved in MC, which allow us to promote National MC program in Israel to the new achievements.

THE 2017 LAW ON THE MEDICAL USE OF CANNABIS AND CANNABINOIDS IN GERMANY

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The German Bundestag, the lower house of parliament, on 19 January 2017 passed a law that legalized the use of cannabis for medicinal purposes. The law took effect in March 2017. It was adopted unanimously by the members of the Bundestag without abstention. Those suffering from serious illnesses such as multiple sclerosis and chronic pain could be prescribed cannabis flowers, cannabis extracts as well as cannabis-based medicines such as the cannabis extract Sativex, dronabinol and nabilone by every German doctor. The law does not limit the possibility to prescribe cannabis and cannabis-based medicines to certain illnesses.

It says patients will only have the right to be treated with cannabis in justified exceptional cases, but patients will not be allowed to grow their own cannabis. "Those who are severely ill need to get the best possible treatment and that includes health insurance funds paying for cannabis as a medicine for those, who are chronically ill if they can't be effectively treated any other way," said Health Minister Hermann Groehe.

The main steps, which finally resulted in the current law, were brought forward by a complaint of 8 patients before the Federal Constitutional Court in 1999. In this context the Federal Administrative Court emphasised the high value of the right to life and physical integrity based on the constitution (Grundgesetz) in the year 2005: "The right of physical integrity cannot only be violated in that bodies of the state themselves produce an assault or inflict pain through their actions. The extent of protection of this fundamental right is also affected if the government takes measures to prevent a medical condition to be cured or at least be mitigated and thereby physical suffering is continued and maintained needlessly." This court decision forced the Federal Government to issue approvals for the use of cannabis flowers to severely ill patients under certain conditions.

State-supervised cannabis plantations will be set up in Germany in the future and until then cannabis will be imported, currently from the Netherlands and Canada. The health ministry said that it is expected that cannabis from Germany will not be available in pharmacies before 2019.

Patients, who are trying to get a cannabis treatment in an increasing number now, are faced with several obstacles. Many doctors are not educated on the issue and remain observant or are sceptical, prices of cannabis flowers in most pharmacies have risen, there are not enough cannabis flowers available in the pharmacies, and covering of costs by health insurances is often denied, so that patients have to pay the higher price of usually about 22-23 € themselves.

MEDICAL CANNABIS IN FRANCE, ANOTHER FRENCH PARADOX

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France was a leading country in herbalist practices until the early twentieth century. But without understandable reason in 1941, the French herbalist diploma was abolished and the uses of plant preparations in the pharmacy slowly disappear as the last herbalist graduated died. Then in 1951 with no scientific argument the French pharmaceutical authority withdraw the Cannabis sativa L. plant from the French pharmacopoeia. In 1970 a law passed, punishing all drug users and their possible political debate, which had, became taboo. In this context, France lost the knowledge about the medical properties of Cannabis, leaving patient to self medication and blocking discussion with physicians to have their situation changed. Therefore in 2009, the first French medical Cannabis association was created, called l' Union Francophone pour les Cannabinoides en Médecine I care, (UFCM I care). Its aim is to make available to health professionals and authority, French content about the latest scientific discovery on the use of Cannabis as medicine. In 2012, l' UFCM I care organized the first medical Cannabis conference in France. However after 6 years of conference, French physicians still remain ignorant on the subject of medical Cannabis. In parallel since 2002 there has been 4 cases of medical Cannabis patients going to justice for their medication. In these cases they were conducted to court trial for cultivating their medicine. They all have been accused guilty but with no jail penalty and no financial fine to pay. But judgment toward patient is still based on case-to-case defense, depending on the patient medical records and his lawyer. In 2013, " Sativex" was allowed by the French medical authority to be distribute in pharmacy for multiple sclerosis but the Haute Autorité Santé (HAS) disagree with "Sativex" distribution price which end up in its none availability in pharmacy. This situation has left patient with no alternative other than auto- cultivation and black market supply. As a paradox, in 2017, France became the country with the highest cannabis user population in Europe, where 22% of its population has used cannabis, and 11% are daily users. In 2017 after new government election the debate is now about giving a fine ticket to Cannabis user, leaving out the question of medical usage. This situation will lead to dangerous amalgam that will expose patient to possible police abuse control. Thus it is urgent to develop a way to protect patient in France to avoid the confusion of Cannabis usage in France between medical and recreational users. To do so, we need to have medical Cannabis training program to teach physician and police force in France to know, how to recognize a medical Cannabis patient. In this way patient could be protecting by his physician and the authority will look in their usage as medical Cannabis necessity, and not as a crime.

BIOCHEMICAL GENOMICS OF CANNABIS STRAIN DIVERSITY

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We are using genomics to elucidate the metabolic pathways leading to the major cannabis metabolites (cannabinoids and terpenes) and to better understand the genetic organization of the genus *Cannabis*. A major experimental approach has been the use of EST and transcriptome data derived from glandular trichomes, the specialized epidermal structures that synthesize cannabinoids. We have successfully applied trichome-focused analysis in combination with classical biochemistry to identify three enzymes of the cannabinoid pathway: hexanoyl-CoA synthetase, olivetolic acid cyclase and an aromatic prenyltransferase. A draft assembly of the ~820 Mbp genome from the marijuana strain Purple Kush, has opened up new avenues for gene discovery as shown by the identification of a novel cannabinoid synthase enzyme, cannabichromenic acid synthase. In addition, the genetic and biochemical basis of terpene production in now under investigation. We have recently used genotyping-by-sequencing (GBS) to analyze the genetic variation in 43 hemp and 81 marijuana accessions. GBS shows that hemp and marijuana are genetically distinct, and provides insight into the differentiation of marijuana into "Indica" and "Sativa" groups. As cannabis emerges from the shadow of prohibition, genomics promises both to clarify its evolutionary history and to accelerate the development of this valuable, multi-use crop.

FUTURE EXPLOITATION IN THE CLINIC OF THE ENDOCANNABINOID SYSTEM AND OF SYNTHETIC DRUGS - MOST PROMISING FUTURE DIRECTIONS

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There is currently considerable interest in the idea of developing new medicines from synthetic compounds that target the endocannabinoid system with high benefit-to-risk ratios and/or that are structural analogues of phytocannabinoids.

Some such medicines may well prove to be one or other of the following types of compound:

Type 1a: a synthetic inhibitor of endocannabinoid (EC) metabolizing enzymes or of EC cellular uptake that, through such inhibition, increases the levels of one or more endogenously released EC at cannabinoid receptors and/or at other pharmacological targets in a manner that enhances EC-induced "autoprotective" effects such as analgesia;

Type 1b: a synthetic positive allosteric modulator (PAM) that increases the potency and/or efficacy with which cannabinoid CB_1 and/or CB_2 receptors are activated by endogenously released ECs, again in a manner that enhances EC-induced "autoprotective" effects;

Type 1c: a synthetic negative allosteric modulator (NAM) or orthosteric neutral antagonist that opposes the activation of CB_1 and/or CB_2 receptors by endogenously-released ECs in a manner that attenuates EC-induced "autoimpairing" effects such as increased obesity;

Type 2: a peripherally-restricted synthetic cannabinoid receptor ligand that, after its administration *in vivo*, cannot enter the brain to produce any unwanted effects by targeting centrally expressed cannabinoid receptors, but can still activate or block CB_1 and/or CB_2 receptors located outside the brain to produce various effects, including therapeutically beneficial ones;

Type 3: a stable or poorly metabolized synthetic analogue of an unstable or rapidly metabolized cannabinoid that possesses one or more pharmacological properties of therapeutic value;

Type 4: a water-soluble synthetic analogue of a water-insoluble cannabinoid medicine, for disorders that would be more effectively or more easily treated with a water-soluble compound.

Just some examples of these types of synthetic compound that might yield, or have already yielded, promising preclinical data, although not yet any human clinical data, are:

Type 1: a CB_1 PAM (GAT211), which, for example, has already been found to produce signs of CB_1 receptor-mediated attenuation of inflammatory and neuropathic pain in mice without also producing either tolerance to such anti-nociception or unwanted CB_1 receptor-mediated effects such as hypothermia or signs of dependence;

Type 2: an as yet unsynthesized peripherally-restricted analogue of the phytocannabinoid, Δ^9-tetrahydrocannabivarin (THCV), as there is evidence that THCV can block renal CB_1 receptors and activate renal CB_2 receptors in a manner that could possibly ameliorate renal nephropathy;

Type 3: a novel synthetic structural analogue of the phytocannabinoid, cannabidiolic acid (CBDA), that has recently been reported not only to be more stable than CBDA, but also to display even greater potency than CBDA as an enhancer of $5\text{-}HT_{1A}$ receptor activation *in vitro*, and as an attenuator, *via* such enhancement, of signs of nausea and anxiety in rats *in vivo*;

Type 4: a potent water-soluble synthetic CB_1 receptor agonist (O-1057) that has already been found to be more potent than Δ^9-tetrahydrocannabinol at producing, in mice, signs of CB_1 receptor-mediated effects such as anti-nociception.

Actual or potential therapeutic benefits and/or risks generated by synthetic compounds of the sort listed above, when they are administered alone or in a combination, will be described.

PROMISING FUTURE DIRECTIONS: CANNABINOID MEDICINES VERSUS CANCER

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A large body of evidence shows that cannabinoids, in addition to their well-known palliative effects on some cancer-associated symptoms, can reduce tumour growth in animal models of cancer and specifically of gliomas. The mechanism of cannabinoid anticancer action relies, at least largely, on the ability of these agents to stimulate autophagy-mediated cancer cell death. Moreover, the combined administration of cannabinoids and temozolomide produces a strong anticancer effect, which correlates with an intense activation of the signalling route that triggers the activation of cytotoxic autophagy. Research conducted in our group has also led to the identification of mechanisms of resistance to cannabinoid anticancer action. For example, up-regulation of the growth factor Midlkine (MK) promotes resistance to cannabinoid anticancer action in gliomas via stimulation of the Anaplastic Lymphoma Kinase tyrosine kinase receptor (ALK); and could be a factor of bad prognosis in GBM patients. All these preclinical findings have facilitated the promotion of a clinical study to investigate the safety and efficacy of the combined administration of the cannabis-based medicine Sativex and temozolomide in recurrent GBM. In this presentation I will discuss these issues and also other possible future studies that may help to clarify whether cannabinoids may be useful as anticancer agents in patients with gliomas or other cancers.

REVERSAL OF AGE-ASSOCIATED COGNITIVE IMPAIRMENTS BY ULTRA-LOW DOSES OF TETRAHYDROCANNABINOL (THC).

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We have previously shown that an ultra-low dose of THC (delta-9 tetrahydrocannabinol) protected the mice brain from a variety of insults (Ref. 1, 2, 3). A single injection of 0.002 mg/kg of THC (3-4 orders of magnitudes lower than doses that induce the conventional cannabinoid effects in mice) prevented the cognitive damage that was induced by either hypoxia, deep anesthesia, MDMA-toxicity, epileptic seizures or neuroinflammation. THC was applied either 1-7 days before or 1-7 days after the insult, thus providing a wide therapeutic time-window. The protective effect of the single injection of ultra-low THC lasted for at least 7 weeks. The protective effect of THC was accompanied by a long-lasting elevation in pERK, pCREB and BDNF in the hippocampus and frontal cortex of the THC-treated mice.

In the present study we tested whether the same ultra-low dose of THC reverses age-dependent cognitive decline in mice. Old (18-24 months) mice performed significantly worse than young (3-4 months) mice in a battery of cognitive assays, including Morris Water Maze, Passive Avoidance, Y maze, Object Recognition and Place Recognition tests. Old mice that had been injected once with 0.002 mg/kg THC performed significantly better than vehicle-treated old mice, and performed similar to naive young mice in all the assays. The improvement in cognitive functioning lasted for at least 7 weeks following a single injection of ultra-low THC.

Sirtuin 1 (SIRT1) is an NAD-dependent protein deacetylase that has been previously shown to be involved in neuroprotection and neuroplasticity. It was found to mediate the protective effects of resveratrol, of melatonin and of caloric restriction, and was suggested to take part in the pathology of various neurodegenerative diseases. In the current study we found that a single injection of 0.002 mg/kg THC elevated the amount of SIRT1-immunoreactive proteins in the hippocampus, the frontal cortex and the cerebellum of old mice for at least 7 weeks.

We further hypothesized that such long-lasting behavioral and biochemical changes might be accompanied by structural changes in the brain. Indeed, MRI (Magnetic Resonance Imaging) revealed structural alterations in the brains of old mice 5 weeks after the injection of 0.002 mg/kg THC: Diffusion Tensor Imaging (DTI) detected a lower mean diffusivity, indicating higher tissue density in various brain regions including the entorhinal cortex, amygdala, cingulate cortex and caudate/putamen. T2 relaxation images demonstrated a larger volume of 3 regions (entorhinal cortex, prefrontal cortex and posterior hippocampus) in brains of THC-treated old mice.

These findings suggest that extremely low doses of THC, that devoid any psychotropic effect and do not induce desensitization, may provide a safe and effective treatment for mild cognitive impairments in aging humans.

References: (1) Behav. Brain Res. 220, 194 (2011); (2) Exp. Brain Res. 221, 437 (2012); (3) J. Neurosci. Res. 92, 1669 (2014)

CANNABIS TREATMENT IN HOSPITALIZED PATIENTS, USING THE SYQE - EXO INHALER - RESULTS OF A PILOT OPEN-LABEL STUDY

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Cannabis is potentially effective in reducing pain, spasticity and chemotherapy induced nausea and vomiting (CINV). However, its use during hospitalization is commonly not feasible, inevitably leading to disruption of treatment continuity and possibly to deterioration in symptoms severity. The SYQE-EXO inhaler delivers precise and reliable doses of cannabinoids (Eisenberg et al 2014 J Pain Palliat Care Pharmacother. 2014;28(3):216-25.) while avoiding personal and environmental hazards of smoking. The current open-label study was aimed to assess the usability, effectiveness and patients' and staff' satisfaction with the use of the EXO inhaler in hospitalized patients, previously using smoked Cannabis at home.
Methods: Hospitalized patients, licensed to use medical Cannabis for the control of chronic pain, CINV, spasticity or a combination were enrolled in the study. Treatment included 2-4 daily doses plus additional SOS dosages of 16mg cannabis (0.5mg THC) per inhalation. Subjects and staff experience and satisfaction with the device and its use were recorded, using a 1-7 scale, where 1 is totally dissatisfied and 7 is totally satisfied. Pain intensity was assessed before and 30 minutes after each inhalation using a VAS 0-10 scale. Wilcoxon Signed Ranked Tests were used for statistical analyses. Results are presented as median [range].
Results: Twelve subjects (6 female), age 41 [27-61] years were recruited to participated in the study. Subjects were treated with Cannabis at a monthly dose of 30 gr [20-100] gr. All subjects were easily trained and continued to use the EXO for the duration of their hospitalization - 4 [3-5] days. No device malfunctions were reported. The number of inhalations prescribed was 4 [3-4], and the number of SOS inhalations allowed was 3 [2-4]. Pain intensity 30 minutes after inhalations was significantly lower than before inhalations 5 [1-5] vs.7.5 [2-9]; Z=-3.059, p=0.002). Subjects ranked their experience and satisfaction with EXO inhaler as 6 [6-7]. This includes an absolute agreement of subjects with statements such as "I would like to continue use the device" and "Inhalation was easy", both receiving median scores of 7 ("absolutely agree"). Importantly patients using the Syqe EXO inhaler consumed significantly reduced amount of daily Cannabis in comparison to their current home use: 54 mg [32-96] mg vs 1000 mg [660-3300] mg per day; Z= -3.230, p = 0.000145). Three subjects reported mild cough immediately following inhalation, which resolved spontaneously within a minute. No severe adverse events were reported.
Conclusions: The present pilot study demonstrated ease of use of the SYQE-EXO inhaler during hospitalization, and high levels of patients and staff satisfaction with its use, with no complications. These results, along with the Syqe- EXO reduced smoking and fire hazards represent a major step forwards in our ability to effectively and safely utilize Cannabis in a hospital setting.

ENDOCANNABINOID INTERACTIONS IN THE REGULATION OF BEHAVIORAL RESPONSES TO TRAUMA

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Introduction: Endocannabinoid signaling affects behavioral responses to traumatic events, however, the specific roles and possible interactions of the two endocannabinoids anandamide (AEA) and 2-arachidonoylglycerol (2-AG) are poorly understood. We assessed the specific effects of AEA and 2-AG on acute responses to a traumatic event and consolidation and extinction of traumatic memories.

Methods: Fear conditioning employing electric foot-shocks was followed by seven consecutive daily contextual reminders and a reminder 28 days after conditioning. AEA and 2-AG signalling was enhanced in Wistar rats by pharmacological blockade of their respective degrading enzymes fatty acid amid hydrolase and monoacylglycerol lipase. Systemic treatments were administered before fear conditioning or before the first contextual reminder. Brain site-specific treatments were administered before fear conditioning to the ventral hippocampus (vHC), prelimbic cortex (PrL), basolateral amygdala (BLA).

Results: Acute fear responses were decreased by local enhancement of AEA signalling in the vHC but not in the PrL or BLA, while this effect was inhibited by enhancement of 2-AG signalling. Interestingly, systemic enhancement of 2-AG signalling before fear conditioning decreased acute fear responses and AEA supressed the effects of 2-AG. Local enhancement of AEA in the vHC and PrL led to strong memory consolidation and this effect was inhibited by 2-AG. In contrast, enhanced AEA signalling in the BLA prevented traumatic memory formation. Enhancement of 2-AG or AEA signalling before the first contextual reminder accelerated traumatic memory extinction.

Conclusion: Taken together, endocannabinoids differentially, interactively regulate behavioural responses to trauma. Acute fear responses are regulated predominantly by 2-AG but under the control of AEA. In the PrL and vHC AEA enhances traumatic memory consolidation under the control of 2-AG but in the BLA AEA inhibits traumatic memory formation. In traumatic memory extinction endocannabinoids have a synergistic role and promote fear relief.

BRAIN KINETICS OF NEUROMETABOLITES DURING CANNABIS INTOXICATION

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Rationale: Cannabis has been demonstrated to cause impairment of cognitive and psychomotor functions during intoxication. Impairments are most prominent in occasional cannabis users but may be subject to tolerance in daily users. Previous research has aimed to define THC blood concentrations above which impairing properties of THC become apparent. However, such studies have generated discussion on the validity of using THC concentrations in peripheral blood to predict impairments in the CNS.

Objective: The present study employed imaging techniques to relate brain kinetics of neurometabolites to behavioral changes during THC serum concentrations above and below a proposed impairment threshold of 2 ng/ml.

Methods: The current project assessed (changes in) brain concentration of GABA and glutamate in the anterior cingulate (AC) and the striatum with magnetic resonance spectroscopy (MRS) and dopamine induced changes in functional connectivity of the nucleus accumbens (FC) during resting state fMRI. Psychomotor vigilance and subjective high were recorded as indicators of cognitive impairment and intoxication. MRS, FC and performance measures were assessed repeatedly during a 2 hr window after administration of cannabis. Blood samples were collected to determine THC concentration in serum. Cannabis and cannabis-placebo were administered to occasional cannabis users by means of a Vulcano vaporizer while they were lying in a 7-Tesla UH-field scanner. One group received a cannabis dosing regimen that produced THC concentration > 2 ng/ml and one received a dosing regimen that produced THC concentrations < 2ng/ml in serum.

Results: As expected, cannabis induced subjective feelings of high and impairment of attention in the subgroup of subjects with THC concentration > 2ng/ml. This group also displayed increments in glutamate (AC and striatum) and GABA (AC) and decrements of FC of the nucleus accumbens. The subgroup that received cannabis doses leading to very low THC serum concentration (i.e. < 2ng/ml) did not show any changes in brain kinetics, performance and subjective feeling of high.

Conclusions: The present data demonstrate that presence of THC concentrations in serum cannot automatically be associated with cannabis induced impairment. The latter was only apparent in subjects with THC serum THC concentration > 2 ng/ml. The present data also indicate that measures of brain kinetics during THC intoxication are feasible and can be used to study the process of neuroadaptation in chronic cannabis users.

THE FUTURE OF ENDOCANNABINOID-BASED THERAPEUTICS

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The major psychoactive constituent of cannabis, Δ9-tetrahydrocannabinol, produces its pharmacological effects by activating cannabinoid receptors in the brain and peripheral tissues. The two primary endogenous ligands for these receptors are the lipid-derived transmitters, anandamide and 2-arachidonoylglycerol (2-AG). Anandamide and 2-AG are released in select regions of the brain and throughout the periphery of the body, and are deactivated via a two-step process consisting of transport into cells followed by intracellular hydrolysis. Anandamide hydrolysis is catalyzed by fatty-acid amide hydrolase (FAAH), while 2-AG hydrolysis is primarily mediated by monoacylglycerol lipase (MGL). In my talk, I will provide a brief outline of drug classes that selectively interfere with the deactivation of anandamide and 2-AG, focusing on their pharmacological properties and therapeutic potential. These agents hold great promise for the treatment of human pathologies such as pain, addiction, anxiety and autism spectrum disorders.

PROMISING INDICATIONS WITH LIMITED CLINICAL EVIDENCE

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Cannabis preparations exert numerous therapeutic effects. They have antispastic, analgesic, antiemetic, neuroprotective, and anti-inflammatory actions, and are effective against certain psychiatric diseases. The first Randomized CT using a cannabis-based medicine was conducted in 1975 to investigate the effects of THC on chemotherapy induced nausea and vomiting. About 140 controlled clinical studies with single cannabinoids, oral cannabis extracts and inhaled cannabis flowers have been conducted over the past 40 years.

However, until today cannabis-based medicines are approved only for a few indications. The cannabis extract nabiximols (Sativex®), an oromucosal spray, has been approved by regulatory bodies in several countries for the treatment of spasticity in multiple sclerosis (in the UK since 2010, followed by several other European countries). In the USA, dronabinol (THC), under the trade name Marinol®, has been licensed for the treatment of nausea and vomiting caused by cytostatic therapy (since 1985) and, in addition, for loss of appetite in HIV/Aids-related cachexia (since 1992). In the USA, Canada, and several European countries, including the UK and Germany, nabilone, under the trade names Cesamet® or Canemes®, has been sanctioned for the treatment of the side effects caused by chemotherapy in patients with cancer.

Most controlled clinical studies have been conducted to treat pain, nausea and vomiting, spasticity in multiple sclerosis and appetite loss. Only a small number of controlled studies have been conducted in other indications, among them, tremor and bladder dysfunction in multiple sclerosis, spinal cord injury, Tourette syndrome, glaucoma, dystonia, irritable bowel syndrome, Crohn's disease, pulmonary disease, and Parkinson's disease.

In a large number of further indications, only (small) uncontrolled studies or case reports are available. Among the indications of patients successfully treated in my medical practice with cannabis based medicines are the following conditions.

Acne inversa, Allergies, Anorexia and cachexia, Anxiety disorder, Asthma, Attention deficit / hyperactivity disorder (ADHD), Autism, Barrett's oesophagus, Bladder spasms (after multiple operations of the urogenital tract), Blepharospasm, Borderline personality disorder, Cervical and lumbar spine syndrome, Cervicobrachialgy, Chronic Fatigue Syndrome (CFS), Chronic pain syndrome after polytrauma, Cluster headaches, Condition after head injury, Crohn's disease, Dejerine-Roussy syndrome after stroke, Depression, Epilepsy, Failed back surgery syndrome, Fibromyalgia, Headache, Hereditary motor and sensory neuropathy with pain and spasms, HIV infection, Hyperhidrosis, Irritable bowel syndrome, Lumbago, Lupus erythematosus, Lyme disease, Migraine, Migraine accompagnée, Mitochondropathy, Multiple sclerosis, Neurodermatitis, Obsessive-compulsive disorder, Osteoarthritis, Painful spasticity in syringomyelia, Paraplegia, Paresis of the brachial plexus, Paroxysmal nonkinesiogene dyskinesia, Polyneuropathy, Posner Castle Man Syndrome, Post-traumatic stress disorder, Psoriasis, Restless legs syndrome, Rheumatoid arthritis, Sarcoidosis, Scheuermann's disease, Sleep disorder, Spasticity in cerebral palsy, Spondylitis ankylosans, Still's disease, Sudeck's dystrophy, Systemic scleroderma, Thrombangitis obliterans, Tics, Tinnitus, Tourette's syndrome, Trichotillomania, Ulcerative colitis, Urticaria of unknown origin.

WHAT QUESTIONS DO CLINICIANS AND PATIENTS HAVE ON A TREATMENT WITH CANNABIS-BASED MEDICINES?

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The increasing availability of information about the potential benefits of cannabis and cannabinoids-based treatments to improve quality of life and symptoms of many diseases whose current treatments have poor results, is bringing to the field more and more physicians trying to do better for their patients, as well patients looking for relief. However, for both actors, the available information is not always of good quality, accurate, reliable, and many times leaves their questions unanswered.

Very often patients get "medical advise" from suppliers and Internet blogs and forums. At least in Latin America, this is the most frequent way for patients to access information about these treatments. The research conducted by Monitor Cannabis Uruguay showed that mass media was the most prevalent way of access among interviewed patients (56.2%), while only 11.9% said they got the information from a health professional.

On the other hand, only 10.6% of the reported ongoing treatments had been recommended by a phycisian. 57% of the patients haven't consulted a phycisian after getting the information for different reasons: they believe it is not an appropriate matter to discuss with a doctor (8.4%), they fear rejection from the doctor (4.2%), they do not have a doctor to follow the treatment (23%), they think they are not prepared to discuss the subject with their doctors because of lack of arguments and information (9.5%), they know their doctors do not support these treatments (9.5%). Briefly, in 57,7% of the cases consultations with a medical doctor did not happen due to barriers in the doctor-patient relationship. Of the interviewees who did consult their doctors (42.2%), almost half of them reported adverse reactions: disapproval, ignorance, skepticism or indifference.

On the other hand, interviews with medical doctors –practitioners and medicine school faculty– showed that they feel unprepared for clinical interventions with cannabinoid-based medicines, that they haven't accessed reliable, science-based, relevant clinical information; and that this is not a subject studied at medicine school.

Some of the patients' questions are related to the potential benefits of cannabinoids-based treatments for their ailments, their compatibility with conventional treatments, kind of products, supply and costs. Doctors have some of the same questions as well as others related to safety and efficacy, indications, interactions, ways of administration, dosing, treatment monitoring, where to get reliable and science-based clinical information, and access to safe products.

To design a relevant medical cannabis educational program we should consider not only the results of scientific research, but also the questions that both doctors and patients have on cannabis and cannabinoids-based treatments.

How do we answer these questions? Where they can get the answers?

Poster Presentations

12-HOUR MONITORING OF THE EFFECTS OF A SYNTHETIC CANNABINOID JWH-018

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Introduction: Spice products, which have comparable effects as marijuana, have become very popular in several countries due to its easy access and portrayed safety. JWH-018, a synthetic cannabinoid, has been reported as an active ingredient of Spice. Unfortunately, little is known about the effects of synthetic cannabinoids and their dose-effect relationship. **Methods**: In the current study, 6 healthy cannabis-experienced volunteers received 2 and 3mg of JWH-018 in a placebo controlled, cross over study. Participants were monitored for 12 hours after administration of the drug, and several cognitive and subjective questionnaires were taken during the day. **Results**: Both doses of JWH-018 were well tolerated, and no serious side effects were reported. Participants reported to feel more 'high' at 1 and 2h after administration. The low dose of JWH-018 impaired performance on a tracking, a divided attention, and a stop signal task. By the end of the test day, participants reported more fatigue after the high dose, while arousal was increased for the low dose. **Conclusion**: This pilot showed that JWH-018 in doses up to 3 mg did not cause serious side effects, that subjective high was rather low and that performance was mildly impaired in occasional cannabis users. Although we expected that the used doses would be comparable to an average dose of cannabis, the demonstrated effects turned out to be lower than expected. Therefore, a follow-up study with higher doses of JWH-018 is currently ongoing.

REPORT ABOUT THE CANNABIS PATIENT RÜDIGER KLOS-NEUMANN

Rüdiger Klos-Neumann

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When Rüdiger Klos-Neumann was 20 years old, he experienced his first cluster headache. In the middle of the night he was torn from the sleep by intense pain which lasted for five minutes. His physician presumed an eye problem and prescribed a pair of glasses but six months later, the next outbreak followed: For one week, Klos-Neumann experienced severe painful attacks every night at the same time, regardless of whether he was asleep or awake. All teeth were removed and newly implanted, hoping to find the source of his headaches. Every time the attacks stopped Klos-Neumann hoped to have found the right remedy. Over and over he was disappointed and his pain came back despite the high-dose opiates and the simultaneous use of antidepressants.

In spring and autumn, the seizures came extremely often - a typical indication for cluster headache – however it took 12 years until Klos-Neumann was diagnosed with this condition by a neurologist.

Cluster headache affects 0.1 percent of the world's population. 55 percent of the patients commit suicide because the intensity of pain and the wait for the next attack became unbearable. For Klos-Neumann things that trigger the attacks are stress, noise, bad light or too little oxygen.

For 20 years, he could continue his profession as a cook and IT expert despite the pain. Then the pain became chronic. The pain phases extended to such an extent that he had to stop working. He was classified as a palliative patient by the doctors as no medication showed any effect.

Then Klos-Neumann started talking with Dr. Franjo Grotenhermen about a possible therapy with cannabis. First Klos-Neumann was skeptical since he had no access to cannabis in pharmaceutical quality and had failed several attempts to try cannabis in the past. He nevertheless received the permission to use cannabis without any problem, still his health insurance denied paying the costs in 2015, although the prescribed cannabis eliminated his cluster attacks completely. The health insurance company was prepared to give Klos-Neumann a monthly pension since he was unable to works in 2016, but they refused to take over the costs for the medication that allowed him to work again. An application to grow cannabis by himself was rejected. If he was unable to pay the cost of 2,000 euros monthly, he let the attacks happen, because there was no alternative to cannabis for him. He also stopped taking any opiates and antidepressants.

Over time, the cook learned that the oral intake was ten times more effective, and he began to cook for himself with cannabis. It became his goal to educate people who are in a comparable situation.

His cooking show was a new professional field. Today, Klos-Neumann cooks on his own channel and shows how to prepare cannabis in different dishes. In addition, he has taken over the management of the media company behind him.

The reimbursement for his medical cannabis was granted immediately after the law change in March 2017. Now Klos-Neumann is provided with medical care. Without cannabis, a strong attack would be triggered within 24 hours. Klos-Neumann's medical history shows how a sufficient supply of medical cannabis can not only significantly improve the patient's condition, but can even make them work again.

EFFICACY AND SAFETY OF A STANDARDIZED OROMUCOSAL FORMULATION OF CANNABIS OIL FOR THE MANAGEMENT OF CHRONIC NON-CANCER PAIN

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Introduction: Pain management is the most commonly reported reason for seeking medical cannabis, which is associated with 64% lower opioid use, fewer medication side effects and better quality of life in patients with chronic pain (*Bonn-Miller et al., Am J Drug Alcohol Abuse, 40(1), 23- 30*). However, therapeutic use of cannabinoids is often hindered by their limited bioavailability and undesirable psychoactivity. The aim of this study is to assess the efficacy and safety of a standardized oromucosal formulation of cannabis oil for the management of chronic non-cancer pain.

Methods: An observational, longitudinal study was conducted over 12 weeks and completed by 49 participants (15 male and 34 female, with an average age of 61.7, ranging between 37 and 90). Inclusion criteria were positive diagnosis of CNCP, willingness to incorporate cannabis to their pain management regime and being a registered cannabis patient in the state of Nevada, USA. Exclusion criteria were having a diagnosis of cancer, history of an allergy to cannabinoid drugs (e.g. dronabinol, Nabilone, Nabiximols), cardiac arrhythmia and pregnancy. All participants gave their consent to be included in the study. A numeric analog scale (NAS) was used to determine self-reported pain, before and at three different time points after treatment (4, 8 and 12 weeks). Additional observations included reduction of opioid medication and occurrence of adverse reactions. Formulations of cannabis oil containing Δ^9-tetrahydrocannabinol (THC), cannabidiol (CBD) and Δ^9-tetrahydrocannabinolic acid A (THCA) were available to participants throughout the study to meet their pain management goals.

Results: An average reduction in NAS pain score of 4.9 points (68%) was observed, with all participants reporting some degree of improvement. Cannabis extracts with various concentrations of THC, CBD and THCA were used, alone or in combination, with comparable results. Duration of the treatment beyond the first week did not further increase the magnitude of NAS reduction. Additionally, 85.2% of participants reduced or discontinued their use of opioid medication and none withdrew from the study due to intolerable side effects.

Conclusions: These results seem to indicate that our oromucosal formulation of cannabis oil represents an effective and safe approach for the management of CNCP. However, a randomized, placebo-controlled, double blind study will be required to further characterize its efficacy and pharmacokinetic profile.

EVALUATION OF CANNABIDIOL OIL PRODUCTS, BASED ON THE GUIDELINES PROPOSED BY JAPAN CLINICAL ASSOCIATION OF CANNABINOIDS (JCAC)

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In Japan, leaves and flowers of cannabis have been made illegal while its stalks and seeds legal since 1948, based on the Cannabis Control Act. Since CNN reported in 2013 that CBD improved severe epilepsy, CBD products have been marketed in Japan. On the other hand, the FDA (USA) tested CBD-related products in 2015, and many were found not to contain the levels of CBD they claimed to contain. Therefore, the Japan Clinical Association of Cannabinoids (JCAC), which we had established in September 2015, proposed a guideline to assure the quality of CBD related products marketed in Japan, and started to provide analytical services to quantify CBD contents under requests from the National Association for Medical Plants (NAMP) in Japan.

Methods: Gas chromatographic system (GC-2014AFC, Shimadzu Corp, Japan) was equipped with a capillary column (12m x 0.20mm, ID 0.33µm, Rxi®-5MS) and a detector (FID). CBD contents in eight commercial CBD products in Japan, nominated as products A-H, were determined and evaluated.

Results: Based on the guidelines of JCAC, CBD products were certified if they contain the levels of CBD to be in the range from -20% to +50% of that they claim to contain. The calibration curve exhibited a good correlation at $r^2 = 0.99999$. The lowest limit of detection was 2 ppm. The differences between the labeled and the actual concentrations of the CBD products (A to H) were determined to be -1.4%, -6.8%, +21.6%, -0.4, +52.7%, -36.3%, +1.2%, and +28.9%, respectively.

Conclusions: According to analytical tests, six out of the eight CBD products were shown to pass the JCAC guideline. We expect that JCAC will contribute not only to scientific and clinical utility of cannabinoids but also to industrial aspects of CBD products.

THE USE OF LOW DOSE WHOLE PLANT CANNABIS OIL EXTRACT FOR THE TREATMENT OF BRAIN CANCER: THREE CASE REPORTS

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The use of medical cannabis for the treatment of all types of cancer dates back thousands of years. The mechanisms of action include anti- angiogenic, anti-proliferative, anti-metastatic, and induction of cancer cell apoptosis. Also, cannabinoids are involved with immunomodulation which may also play a role in cancer treatment. Specifically, cannabis use for brain cancer treatment may be useful since cannabinoids cross the blood-brain barrier where conventional therapies may not.

The objective of this study is to report the results of the treatment of three separate patients with brain cancer, either metastatic or primary with the use of low dose whole plant cannabis oil extract administered alone or in conjunction with other cancer therapies.

Methods: Three patients were treated with medical cannabis. Patient one has leptomeningeal metastatic ALL in hospice. Patient two has an inoperable, temozolomide resistant glioblastoma, Patient three has a temozolomide resistant anaplastic astrocytoma grade 3. Each patient is treated with low dose cannabis oil extract containing both acid and decarboxylated cannabinoids: THCA 0.54mg, THC 0.43mg, CBDA 0.055mg, CBD 0.072mg, CBN 0.03mg, and CBG 0.044mg per 1 ml-administered 1ml sublingually and titrated as recommended. Benchmarks were defined and followed for each patient.

Results: *Patient one*, diagnosed with metastatic ALL was in hospice. The original goal was to mitigate cephalgia and to improve the quality of life by reducing the amount of required opioids. The treatment resulted in the complete replacement of opioids with low dose cannabis oil and transitioned the patient from hospice to remission.

Patient two, diagnosed with glioblastoma showed an improvement in sensorium and physical abilities after two days of treatment with low dose cannabis oil. Two weeks after the commencement of cannabis oil treatment the patient had a repeat MRI that revealed the mass to have undergone central cystic degeneration. The patient was subsequently treated with radiation therapy in addition to the cannabis oil and nine months later a repeat MRI revealed a stable slightly smaller tumor. Three months later, the patient continues with low dose cannabis oil only with no further tumor growth.

Patient three, diagnosed with anaplastic astrocytoma grade 3 was treated with temozolomide for six months after initial diagnosis. Repeat MRI revealed a larger tumor. The chemotherapy was changed to Lomustine and treatment with the cannabis oil commenced two weeks after initiation of Lomustine. After six weeks of combination Lomustine and cannabis oil treatment an MRI revealed tumor size reduction. Also, the patient reports improvement of sensorium, activity, and speech.

Conclusions: Cannabis has been reported to cause programmed cell death as one of its mechanisms of action against cancer cells. Cannabinoids have also been shown to play a role in anti-angiogenesis, anti-proliferation and prevention of metastasis in addition to mitigating the symptoms that result from conventional therapy such as anorexia, nausea and vomiting, anxiety, and insomnia. Cannabis has also been shown to be a successful adjunct as treatment in combination with other traditional therapeutic modalities. In these case reports, two patients were not being treated with traditional medical therapies when they received a significant response with cannabis oil. The third patient experienced tumor reduction as well as physical improvement with a combination of chemotherapy and cannabis oil. No reports of adverse side effects from the cannabis oil treatment.

REVIEW OF THE EVIDENCE ON DIETARY CANNABIS AS AN ANTI-INFLAMMATORY AGENT

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Inflammation is the biological response to harmful stimuli; chronic inflammation causes most of the major killer diseases in industrialized Countries including cancers, cardiovascular issues, diabetes & many other auto-immune or neurodegenerative conditions. Substantial evidence indicates that various parts of the Cannabis plant, consumed in their raw, un-decarboxylated state, could offer substantial benefit in prevention and treatment of chronic inflammation. The seeds of Cannabis Sativa are unique in the plant kingdom since they are composed of 65% Edestin. Edestin protein boosts the immune system by building immunoglobulins and increases the DNA-repairing activities. In addition, Cannabis seeds contain more than 80% Polyunsaturated Fatty Acids(PUFAs) in the optimal ratio of 3.75:1 (omega 6:3), (*Matthäus and Brühl, 2008*). The essential fatty acids contained in Cannabis include Linoleic Acid, alpha-Linolenic Acid, and gamma-Linolenic Acid, which are critical for reducing inflammation. (*Callaway, 2004*). Cyclooxygenase enzymes (COX-1 and COX-2) catalyse the production of prostaglandins from Arachidonic Acid. Prostaglandins are important mediators in the inflammatory process and their production can be reduced by COX-inhibitors. Unique flavonoids to the Cannabis plant (the cannaflavins) show a consistent prostaglandin inhibition (*Barett et al.,1986*). Prostaglandin E-2 (PGE-2) overproduction enhances vascular permeability, worsening inflammation and is the target of nonsteroidal anti-inflammatory drugs (NSAIDs). Cannflavin A causes over 90% inhibition of PGE-2 release, without displaying toxicity. The mean IC_{50} on PGE-2 of cannflavin resulted 30 times more potent than aspirin. Other flavonoids contained in Cannabis but not exclusive to it, such as Apigenin and Quercetin, also exhibit potent antiprostaglandin activity. Apigenin specifically inhibits tumour necrosis factor (TNF)-induced inflammation. (*Gerritsen et al.,1995*) β-Caryophyllene (BCP) is a common sesquiterpene found in Cannabis; It is the first identified "food-stuff" to directly activate CB2R and exerts its anti-inflammatory property by binding to them. BCP prevents prostglandins (PG) production, by blocking COX-2 mRNA expression. BCP also inhibits pro-inflammatory cytokines TNF-α, IL-1β, and IL-6, as well as production of Nitrogen Oxide (NO). β-myrcene is a monoterpene also produced by Cannabis which shows significant anti-inflammatory effects via inhibition of COX and hyperalgesia induced by PGE-2. β-myrcene was found to have immunoregulatory activity, inhibiting the production of NO, as well as cytokines Interferon gamma (IFNγ) and Interleukin-4 (IL-4). The anti-inflammatory properties of THCA are mediated by inhibition of COX-1 and COX-2, and via interaction at various degrees with vanilloid receptors (TRPM8, TRPA1, TRPV4) as well as by inhibiting endocannabinoid breakdown by blocking the enzyme MAGL. CBDA also shows promising anti-inflammatory effects, as it selectively inhibits COX-2 activity (Takeda, 2008)

Methods: This report aims to synthesize the existing literature and comment on the current state of evidence regarding compounds which are contained in raw Cannabis. Studies were included if they **a)** were published in English, **b)** were published in a peer-reviewed journal, **c)** were describing anti-inflammatory effects of molecules produced by the Cannabis plant. Among these, were excluded all publications describing compounds which require decarboxylation in order to be viable in the plant.

Results: **1**) Evidences show safety on dietary consumption of Cannabis seeds, fresh leaves or flowers **2**) Effects of raw Cannabis are not centrally mediated **3**) Many of the molecules contained in the raw fresh plant show therapeutic potential as anti-inflammatory drugs **4**) Most of these compounds are lost upon heating/decarboxylation of the plant, the most common administration form.

Conclusions: We conclude from these findings, that the effects of raw Cannabis are devoid of centrally-mediated effects and that their consumption could provide a powerful source for an anti-inflammatory diet. It emerges a clear need for clinical trials on the dietary use of raw Cannabis in prevention and treatment of inflammatory conditions.

TELEMEDICINE AS THE POSSIBLE FUTURE OF MEDICAL CANNABIS CONSULTATION IN EUROPE

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Summary:
Despite the increasing awareness of the benefits of medical cannabis, patients in Europe are struggling to access professional advice and medications. Is telemedicine one of the solutions?

Hypothesis:
The digital revolution in healthcare is picking up space; advanced smartphones, fast internet connections, secure online communication and transmission of medical data are transforming the healthcare sector. This goes hand in hand with medicinal cannabis in Europe. Telemedicine could transform the way patients receive cannabis treatments and prescriptions.

Areas of research:
- The technologies regarding telemedicine, 21 platforms and systems have been analyzed.
- The legal aspects of telemedicine concerning the interaction patient-clinician.
- The legal aspects and process of prescribing cannabis medications using telemedicine.
- Clinician liability in the case of medical cannabis.
- The supply chain of cannabis medications.
- The information we collected during one year of interviews with patients, aoctors and associations from The Netherlands, Spain, Czech Republic, Italy, Germany, Estonia, Finlandia, Bulgaria, Belgium and France.

Results:
There is a limited legal support for patients and doctors in the medical cannabis sector; limited access to cannabis medications and limited number of clinicians specialized in Medical Cannabis. Medical Cannabis is legal and regulated in the Netherlands by The Office for Medicinal Cannabis (OMC) Ministry of Health, Welfare and Sport. Telemedicine it is an effective medical tool approved and regulated in the Netherlands by KNMG (The Royal Dutch Medical Association), The Netherlands Standardization Institute: Quality of Telemedicine NEN 8028-2011 and the European Union Directives 2011/24/EU, 95/46/EU, 2000/31/EC and 2002/58/EC

Conclusion:
If using the approved and regulated technologies and following the consultation protocols, Telemedicine is an effective medical tool to treat cannabis patients in Europe; but the Telemedicine service need to go together with legal support for patients and doctors and offer an easy access to cannabis medications. It is not possible to have a global strategy for the whole Europe, different regulations apply concerning Medicinal Cannabis and Telemedicine that need to be address on a country base.

STRATEGIES FOR THE VAPORIZATION EFFICIENCY EVALUATION OF THE DA VINCI ASCENT™ PORTABLE VAPORIZER

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Introduction: In Switzerland, on one hand, cannabis preparations containing a significant dose of delta-9 tetrahydrocannabinol (Δ^9-THC) can be administered for therapeutic purposes in a very limited number of indications. On the other hand, the recreational use of cannabis containing less than 1% Δ^9-THC and varying weight proportions (typically between 5 and 20%) of cannabidiol (CBD) is legal. This cannabis is usually mixed with tobacco and smoked in joints. The smoke contains noxious tars and gases that are byproducts of cannabis combustion. Inhalation of cannabis vapors generated below the combustion point ($\approx 235°C$) should strongly reduce the production of adverse toxic compounds. Lowering the temperature could also decrease the aerosolisation efficiency of cannabinoids. Vaporizers could be effective harm-reduction tools but their efficiency should be better determined.

Aims: In this context, we used the Da Vinci Ascent portable vaporizer as a test device to evaluate the decarboxylation yield of the acid precursors of cannabinoids as well as their vaporization efficiency obtained with 3 cannabis strains under various experimental settings.

Methods: 5 grams of cannabis flower tops (obtained from Bedrocan NL) were chopped into a relatively fine powder. The vaporizer was loaded with 200-350 mg of cannabis powder. Then, the vaporizer was connected to twin sampling supports (active charcoal or XAD-2) or to Drechsel glass impingers filled with 20-50 mL of trapping solvent and to the air pumps via rubber tubes. Several parameters were investigated (puffing volume (70-250-600 mL in 5 sec), number of puffs (1-30), vaping temperature (190-220°C), horizontal or vertical position of the vaporizer). To mimic a chimney effect, a residual flow was maintained at 1.3 ml / sec between successive puffs when the vaporizer was set in the vertical position. The cannabinoid concentrations in the heated residue and in the trapping cartridges and solvents were determined with HPLC-DAD. The vaporizer glass tubes, the rubber tubings were also analysed. Identity of cannabinoids in silylated extracts was confirmed with GC-MS analysis.

Results: **1)**. The cannabis flower tops contain almost no neutral cannabinoids and no cannabinol (CBN), **2).** The acid precursors of cannabinoids were fully decarboxylated, **3).** Negligible amounts of cannabinoids were found in the trapping sorbent or solvent at low vaporization temperature (190°C) while significant amounts were recovered at 220°C. **4).** The highest yield was observed with a vaporization temperature of 220°C and a puffing volume of 600 mL, **5.)** Increasing the number puffs resulted in the formation of higher amounts of CBN in the heated residue, especially at 220°C **6.)** Large amounts of cannabinoids were trapped on the glass walls of the T-tube vapor collector. Few were recovered from the rubber tube connectors.

Conclusions: We conclude from these findings, that **a**) the Da Vinci Ascent vaporizer is characterized by relatively poor vaporization efficiencies and **b**) that optimization of the vaporization conditions requires laborious and time-consuming tests, **c**) the design of the device could be improved by a better vapor delivery system, **d**) the design of the vaporizer appears to prevent any overdosage of cannabinoids, **e**) the slow vaporization process should facilitate the titration of the desired effects.

ANTILEUKEMIC EFFECT OF CANNABINOIDS DERIVATIVES: A NEW THERAPEUTIC GROUP IN ACUTE MYELOID LEUKEMIA (AML)

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AML represents a heterogeneous group of diseases caused by a clonal disorder resulting from genetic alterations in hematopoietic stem cells. Treatment of AML is still based on the combination of an anthracycline and cytarabine, developed 40 years ago. Therefore, the development of new therapeutic strategies is an unmet medical need for these patients. Here, we tested the effect of the cannabinoid WIN-55,212-2 in AML in vitro and in vivo and studied the molecular signaling pathways involved in this effect. Moreover, we synthesized a new family of nine cannabinoids that are specific to CB2.

To assess the anti-leukemic effect of these cannabinoids, we analyzed cell viability by MTT and flow cytometry assays using six human AML cell lines, primary cells from healthy donors (hematopoietic progenitor cells (HPC) and lymphocytes) and blasts from AML patients. Mitochondrial damage was analyzed by flow cytometry using TMRE and by MitoSOX™ Red. In addition, we determined the expression of different proteins to elucidate the molecular signaling pathways involved. Moreover, we analyzed ceramide levels, a membrane lipid associated with death/survival cell processes, and other sphingolipids by LC-MS/MS and immunohistochemistry. Finally, NOD/scid/IL-2R gammae null mice were xenotransplanted with HL60 cell line. Once the presence of leukemic engraftment was confirmed in bone marrow, treatment with vehicle, WIN-55,212-2 at a dose of 5 mg/kg/day or citarabine was administered. Also we tested the effect of these compounds on normal hematopoiesis by treating healthy BALB/c mice and the levels of sphingolipids in cell and plasma were studied.

Cannabinoids induced a potent pro-apoptotic effect on AML cell lines and primary leukemic cells, which was not observed in normal HPC or lymphocytes from healthy donors. Fragmentation of PARP and activation of caspases 2, 3, 8 and 9 were confirmed by Western Blot. The pro-apoptotic effect of cannabinoids on AML cells was abolished upon co-culture with either CB2 receptor antagonists or with pancaspase inhibitors. Other proteins involved in this effect were p-AKT, p-ERK 1/2, p-38 and p- JNK. Also studies on p-PERK, p-IRE1 and CHOP confirmed an increased endoplasmic reticulum stress upon exposure to cannabinoids. Also we confirmed a very early mitochondrial damage in leukemic cells which was not observed in normal HPC. Remarkably, we observed significant differences in amounts of certain sphingolipids in untreated versus treated leukemic cells such as ceramide C16:0, C18:0 and C18:1. In vivo studies demonstrated a significantly increased survival among mice treated with WIN-55,212-2 as compared to both the control group and the group treated with cytarabine and we confirmed that cannabinoids did not affect the viability of the different sub-populations of HPC and, moreover, an increased platelet count was observed in treated mice.

Our findings indicate that cannabinoids display a highly selective proapoptotic effect against leukemic cells. Several pathways are involved in this effect, the modification in the sphingolipids pattern playing a main role.

OBSERVATIONAL SURVEY STUDY OF CURRENT AND POTENTIAL CANNABINOID THERAPY USERS

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Background/Aims: Medicinal use of cannabis is being widely legalized, and provides the opportunity for observational data collection in the absence of controlled clinical trials. A convenience sample of individuals from across the United States was recruited to study basic demographic and health profiles of patients currently using cannabinoid products for therapeutic purposes versus those who were interested, but had not yet started cannabinoid therapy.

Methods: Participants (N = 703) had a mean age of 37 years; 61% were female, and 82% were Caucasian. 424 patients were using cannabinoids for at least one health condition. 279 patients were considering use of cannabinoids, but had not started at the time the survey was completed. Participants were assessed for demographics, primary medical condition, number of emergency room (ER) visits, patient quality of life (QOL), number of medications used, number of sick days, quality of sleep, and average pain over the past 30 days. T-tests and chi-square analyses were used to assess differences between cannabis users and non-users on study outcomes.

Results: Current cannabinoid users were older than non-users ($M = 38.58$, SD = 21.28 vs. $M = 34.38$, SD = 20.11; t(701)= -2.61, p = 0.009), were more likely to have a primary medical condition of chronic pain (χ^2(1, N=703 = 4.40, p = 0.045), and less likely to have a neuropsychiatric condition as the primary medical concern (χ^2(1, N = 703) = 4.31, p = 0.038). Current cannabinoid users reported fewer ER visits ($M = 0.4$, SD = 0.77 vs. $M = 0.74$, SD = 1.31; t(172) = 2.49, p = 0.014) and fewer sick days taken from work/school ($M = 4.18$, SD = 8.15 vs. $M = 5.81$, SD =9.65; t(447)= 2.14, p = 0.033) in the past month compared with non-users. The differences in ER visits and sick days was not due to the disparity between groups on the rate of chronic pain or neuropsychiatric disorder as the primary medical condition. No significant differences between cannabinoid users and non-users were observed for the number of OTC or prescription medications, or for individual item ratings of patient QOL, quality of sleep, or average pain rating in the 30 days prior to survey completion.

Conclusions: This data suggests that there may be some added benefit of cannabinoid use on current health care utilization and outcomes for certain health conditions. This study is currently ongoing and follow-up assessments are being collected at 3-month intervals in order to track changes in health over time. The ultimate aim of the study is to prospectively evaluate the impact of cannabinoid use on health-related outcomes and to identify specific health conditions and cannabinoid product characteristics that are associated with greater therapeutic benefit and/or risk of adverse effects to specific subgroups of patients.

COMPARATIVE PHARMACODYNAMIC INVESTIGATION OF ORAL, SMOKED, AND VAPORIZED CANNABIS

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Background: In the U.S., a burgeoning cannabis marketplace exists that offers a growing number of consumable cannabis goods and products intended for use via a variety of methods of administration. Few controlled studies that have been conducted using administration methods other than smoking. We conducted a series of studies to directly compare the dose effects of cannabis following oral, smoked, and vaporized routes of administration.

Methods: The comparative pharmacokinetic and pharmacodynamic effects of cannabis were assessed in healthy adults at 0, 10mg, and 25mg THC dose across routes of administration. 17 participants completed all doses within each route. Participants had a history of cannabis use, but had not used cannabis for at least one month prior to randomization. Outpatient sessions were conducted 1 week apart. Pharmacokinetic and pharmacodynamics assessments were obtained at baseline and for 8 hours following drug exposure. Analyses compared active dose conditions with placebo, and the same doses were compared across routes of administration. Correlations between behavioral measures and cannabinoids in blood and oral fluid were evaluated.

Results: Dose dependent drug effect ratings, cardiovascular effects, and cognitive performance effects were observed across routes of administration. Peak drug effects occurred within fifteen minutes for inhaled cannabis followed by a gradual return to baseline. In contrast, oral cannabis drug effects onset +60-90min post-administration and remained at peak levels for a longer period of time. Cardiovascular and cognitive performance effects had a different time course with cardiovascular effects occurring more immediately (peak effect at +90min) compared with subjective drug effects (peak effect at +180min) and cognitive performance impairment (peak effect at +300min). The magnitude of peak drug effects was comparable across the smoked and oral routes of administration, but greater following vaporized cannabis administration. Blood cannabinoid levels were significantly correlated with subjective drug effect ratings and inversely correlated with some performance tasks. Oral fluid THC was significantly correlated with self-reported Drug Effect following smoked (r = 0.21) and vaporized (r = 0.26) cannabis, but not oral cannabis. Oral fluid THC was not significantly correlated with psychomotor, divided attention, or working memory performance following any route of administration.
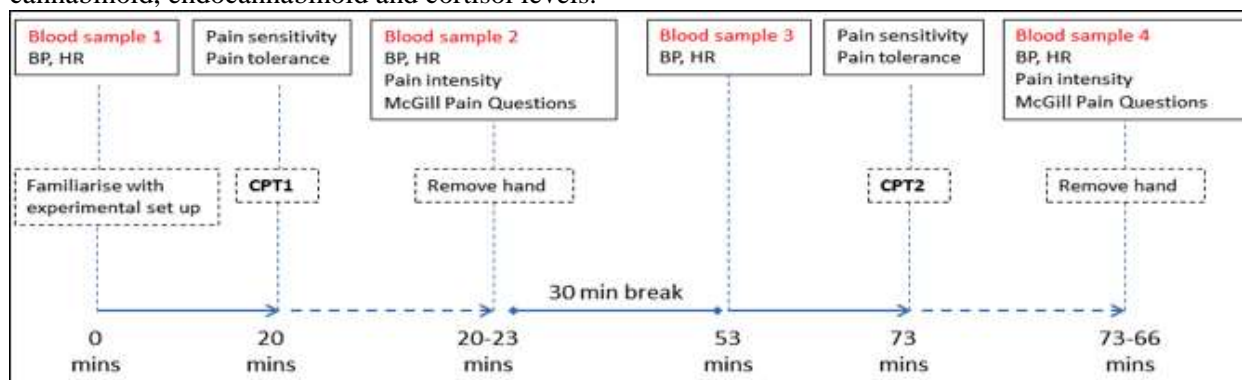
Conclusion: Significant variability in the pharmacodynamic effects of cannabis was observed across doses and as a function of route of administration. At the same doses, the magnitude of peak drug effects was comparable for both oral and smoked, but higher for vaporization, suggesting it is a more efficient route of cannabis delivery. Blood cannabinoids were better biomarkers of acute drug effects than oral fluid cannabinoids, but neither was consistently well correlated with performance on cognitive tasks.

A PILOT STUDY OF THE EFFECTS OF CHRONIC CANNABIS USE ON PAIN SENSITIVITY, PAIN TOLERANCE AND PLASMA ENDOCANNABINOID LEVELS

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INTRODUCTION: Chronic opiate users often exhibit hypersensitivity to painful stimuli, most likely due to downregulation of endogenous opioid pain-control mechanisms. Cannabis is frequently used for chronic pain and it is possible that chronic cannabis use might downregulate endocannabinoid pain control systems leading to pain hypersensitivity. To address this hypothesis, we conducted a small pilot study to examine if regular cannabis users exhibit differential sensitivity and tolerance pain relative to non-cannabis using controls on the Cold Pressor Test (CPT). We also examined plasma cannabinoid, endocannabinoid and cortisol levels.

METHODS: Twenty-one males were recruited to the study (10 cannabis, 11 control). The cannabis users smoked a $\bar{x}$ of 6.3 grams per week and smoked for a $\bar{x}$ of 13 years. All gave negative saliva test results for THC on arrival at experimental session, indicating abstinence from cannabis for approximately 12 hours prior to entering the experiment. The sequence of experimental events are shown above, and involved two CPTs with blood samples taken before and after each test.

RESULTS: Results showed that cannabis had greater pain tolerance than controls on the second CPT (p=0.044), but not the first (p=0.182; Figure 2). Similarly, cannabis users showed a trend towards longer time to reporting pain than controls on CPT2 (p=0.057), but not CPT1 (p=0.89). There were no significant differences in ratings of the intensity of pain between groups or CPTs. Interestingly, cannabis users displayed elevated plasma levels of anandamide (p=0.016), oleoylethanolamide (p=0.008), linoleyl-ethanolamide (0.011), and palmitoylethanolamide (p=0.037) relative to controls. There were no group differences in 2-arachidonoylglyceraol levels. Some of the endocannabinoids increased over time, possibly in response to CPT stress. Anandamide was significantly elevated over controls at bloods 3 and 4 (flanking CPT2, post hoc p=0.007 and 0.003 respectively). Palmitoylethanolamide was elevated compared to controls at bloods 2 and 4 (immediately after both CPT immersions, post hoc p = 0.041 and 0.037 respectively). Plasma levels of THC and THC-COOH in cannabis users did not change with CPT exposure. Cannabis users had lower plasma cortisol than controls (p=0.042), and only controls showed significantly increased cortisol in response to the two CPTs (p=0.041).

CONCLUSION: These pilot results, somewhat unexpectedly, show that cannabis users had *greater* pain tolerance and reduced pain sensitivity than controls, blunted basal and stress-induced cortisol responses, as well as elevated basal levels of some endocannabinoids.

ANALYSIS OF REGULATORY IMPROVEMENTS AND SETBACKS FOR MEDICAL CANNABIS PROGRAMS AND PRODUCT SAFETY STANDARDS

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Patient Focused Certification (PFC) is a 3rd party certification program focused on *Cannabis* product safety. PFC was developed by Americans for Safe Access (ASA) a medical *Cannabis* advocacy organization. ASA set the standards in the U.S. for medical *Cannabis* product safety and best practices for manufacturing, dispensing, cultivation, and laboratory operations. The PFC program is working around the world to implement existing standards and best practices for patients, providers of medical care, companies, regulatory bodies and legislators.

Recently, PFC and international partner groups have started incorporating European Union standards for hemp and cannabis. This presentation will provide an update on cannabis regulations in the US and Europe, data on cannabis dispensary staff training in the US, as well as a data grading regions in the US and Europe, with a medical cannabis program, under a 400 point assessment with a 5 general categories: Patient rights and civil protections, access to medicine, ease of navigation, functionality, and consumer safety (see example of the analysis below).

DEVELOPMENT OF THE BEDROMEDIC® AS A CERTIFIED VAPORIZER FOR THE INHALED USE OF MEDICINAL CANNABIS

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Vaporization offers patients who use medicinal cannabis the advantages of the pulmonary routes of administration (rapid delivery into the bloodstream, ease of self-titration, and concomitant minimizing the risk of over- and under-dosing) while avoiding the respiratory disadvantages of smoking. This presentation focuses on the process of development of a new vaporizer - Bedromedic® - as a medical device.

Methods: Different aspects of the vaporizer were tested:

1. User comfort

Vaporizing may produce discomfort to users. Most commonly reported problematic aspects are: heat on the lips, throat dryness, lung coughing and nose itching. Feedback was collected from users in order to improve the inhalation procedure.

2. EMC and ES security

The Bedromedic vaporizer must be fully secure for patient use. The international standards for electromagnetic compatibility (EMC) and electrical security (ES) meet the minimum criteria for safe and correct operation of the medical device.

3. Heating speed

Based on the validation results of administration of Bedrocan and Bediol cannabis varieties with the use of the miniVAP, Hermes Medical Engineering improved the heating core for the Bedromedic vaporizer in order to guarantee a quick heating time.

4. Power consumption & RoSH

It is important for a proper medical device to reduce the power consumption and the restriction of hazardous substances (RoSH) in order to reduce the greenhouse emissions and protect the environment.

5. Maximum vapor amount per inhalation

Long and intense inhalations usually result in coughing and expectoration for users. A smaller heating core and a specific design of the mouthpiece may help to limit the heat and increase comfort.

Results:

Users described different interactions, mainly due to the excess of heat and high density of the vapour, and the presence of irritant active ingredients in the pulmonary route. By improving the size of the heating element and the design of the mouthpiece, the temperature and density (vapour amount per inhalation) of the vapour was reduced. Also, the heating time and power consumption was decreased significantly.

Moreover, the electrical and electronic design of the vaporizer successfully completed the tests required by the international standards of EMC, ES and RoSH.

Conclusions:

The medical vaporizer Bedromedic has been designed for reliable administration of medicinal cannabis in terms of dosing and user security. The device complies with the international standards for medical devices, guaranties comfort to the user in the process of inhalation, and reduces the impact on the environment. As a consequence, the Bedromedic vaporizer meets the criteria for a medical device.

CHRONIC PAIN TREATMENT WITH CANNABIDIOL IN KIDNEY TRANSPLANT PATIENTS IN URUGUAY

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Chronic pain is a major therapeutic problem in kidney transplant patients due to the limitation in NSAID use caused by its nephrotoxicity. There is benefit of the modulation of the endocannabinoid system in the treatment of chronic pain. The use of cannabidiol (CBD) in kidney transplant patients has not been communicated previously.

Objective: We aimed to assess the effect, safety and possible drug interactions in kidney transplant patients treated with CBD for chronic pain.

Methods: We assessed patients who receive progressive doses from 50 mg to 150 mg twice a day for 3 weeks of CBD for treatment of chronic pain. Weekly visits where we determine creatinine, blood count, functional and liver enzyme and drug levels.

Results: We assessed 7 patients mean age 64.5(58-75), who had asked for CBD pain treatment.

Table1. Base line characteristics in day 1 and 21 per patient

	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5		Patient 6		Patient7	
Age	75		58		61		60		60		73		65	
Sex	F		M		F		M		M		F		M	
Pain Cause	Fibromyalgia		Osteoarticular		Fibromyalgia		Osteoarticular		Osteoarticular		Osteoarticular		Neuropatic	
Day	1	21	1	21	1	21	1	21	1	21	1	21	1	21
Creatinine mg/dl	1.10	1.04	1.03	1.12	0.92	0.89	1.14	1.16	1.94	2.8	2.07	1.95	2.39	2.36
Hemoglobin g/dl	11.4	10.7	13.4	13.1	12.4	12.9	15	14.3	11	10.2	11.5	10.9	14.7	14.8
Leucocytes mm3	3990	4370	7080	8960	4480	5280	8830	10850	7420	6360	12900	11760	10100	12600
Platelets(10^3 m3)	185	174	215	237	182	199	248	245	189	174	306	265	157	213
TGO/TGP (mg/dl)	14/11	14/10	14/18	16/22	20/12	19/12	16/9	12/8	16/11	15/11	25/19	19/16	19/16	16/19
Tacrolimus (ng/ml)	10.1	6.5	7.4	2.8	14.4	16.7	9.7	9.8	7.8	13.8	-----	-----	-----	-----
Cyclosporine (ng/ml)	----	----	----	----	----	----	----	----	----	----	355	332	261	291

Initial dose of CBD was 100 mg/day, CBD dose reduction to 50mg/day has been done on day 4 in patient n°1 due to persisting nausea. Tacrolimus dose reduction in patient n°3 has been done in day 4 and 7 due to persisting elevated levels (before CBD) and itching and in day 21 in patient n°5. Tacrolimus levels decreased in patient n°2 but were normal in the control one week later. Patients in cyclosporine were stable. Adverse effects were nausea, dry mouth, dizziness, drowsiness and episodes of intermittent heat, which required CBD dose decrease in 2 patients. 2 patients had total pain improvement, 4 had a partial response in the first 15 days and in one there was no change

Conclusion: During this period of follow up, CBD was well tolerated and we didn't find any severe adverse effect. Plasma levels of Tacrolimus had a variability that requires longer follow up to assess effect, safety and possible drug interactions. In the 2 patients with cyclosporine, CYA plasma levels were steady. There is need to follow up more patients. Meanwhile we recommend weekly drug serum determinations during the first month of CBD treatment followed by monthly determination.

SUBCHRONIC EXPOSURE TO CANNABINOID AGONIST R(+)WIN55,212-2 ALTERS STOPPING MECHANISM OF ABSENCE SEIZURES IN RATS

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Introduction: WAG/Rij rats are a well-validated genetic model of absence epilepsy. All animals develop spontaneous absence seizures after 2-3 months of age, which are characterized by 7–10 Hz spike-wave discharges (SWDs), the electroencephalographic hallmark of these seizures (1). A single acute exposure to the cannabinoid agonist R(+)WIN55,212-2 (*WIN*) initially reduces the number of absence seizures in rats, but only in the first 3 hours after the injection; this decrease is followed by an increase in the mean SWD duration for at least 8 hours after injection (2). Since drug effects of repeated use are of the utmost relevance clinically, in the present study the effects of subchronic administration of R(+)WIN55,212-2 on SWDs in adult WAG/Rij rats were investigated.

Methods: 16 male rats were used: 8 were injected with R(+)WIN55,212-2 (6 mg/kg in 3 ml/mg olive oil, s.c.), and 8 with the same volume of olive oil. Injections took place 3 times a week during 4 weeks. The EEG was recorded before treatment (*baseline*), directly after the first treatment (*wk 0*), and subsequently after 2 and 4 weeks, each time for 24 hours, and SWDs were quantified.

Results: The CB1 agonist did not affect the number of SWDs, if averaged over 24 hours. However, the WIN-treated group showed an increase in the SWD duration: 12.1s (SD 1.8) compared to 8.7s (SD 1.4) in controls, directly after the first treatment in week 0, and 12.6s (SD 3.4) compared to 6.2s (SD 2.1) in week 2. In week 4, this increase in mean duration was no longer observed. Interestingly, in week 0, an increased percentage of long (> mean + 2 SD) was observed. In the WIN treated group, this accounted for 12.5% of all SWDs, compared to 3.4% in the controls.

Conclusion: The initial increase of the mean SWD duration, together with the appearance of extremely long SWDs suggests that the SWD stopping mechanism might be influenced by the CB1 agonist. The reduction of this increase in the 4th week of treatment, suggests either pharmacodynamic tolerance, e.g. to down-regulation/desensitization of the CB1-receptor (3) and/or it might point to pharmacokinetic tolerance for the drug (4).

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TREATMENT WITH CANNABIS FLOWERS IN ADULT ADHD

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Introduction: Attention deficit hyperactivity disorder (ADHD) may persist into adulthood and become treatment resistant to standard medication. Many patients report on a symptom relief with Cannabis. Although with noticeable symptom reduction associated, their experience is mainly restricted to THC-predominant blackmarket strains of unknown quality. With an approval by the Federal Institute for Drugs and Medical devices it was possible to buy Cannabis flowers from the pharmacy with a specific Cannabinoid-composition. Due to the recent change in legislation (March 2017), Cannabis flowers can be regularly prescribed if guideline-therapy is not effective or showed too many side effects.

Methods: The katamnestic data between 2015 and 2017 of 100 adult ADHD-patients medicating with Cannabis flowers were analyzed regarding their preferred strains, dosage of single and daily intakes, routes of administration and their experiences with CBD products on key symptoms. Changes in quality of life, benefits in social and work environments and effects on comorbidities are described.

Results: With the intake of prescribed Cannabis flowers patients experienced an improvement of the ability to focus and a stabilization of their mood. Cannabis flowers containing a relevant amount of Cannabidiol led to a positive influence on impulsiveness and agitation. Treatment was limited due to severe costs of Cannabis flowers with lack of reimbursement and the reduced availability of different strains after changes in legislation.

Conclusion: The effects of Cannabis flowers in ADHD are clinically evident, whereas the benefits of relevant amounts of CBD are still unknown to many patients. Further research on the basis of randomized, controlled trials with standardized Cannabinoid-medication is reasonable to substantiate the indication ADHD and should help to encourage the clinical implementation.

A PROSPECTIVE NATURAL HISTORY STUDY OF CANNABINOID USE AMONG PATIENTS WITH EPILEPSY

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Introduction. Epilepsy is a class of serious neurologic disorders that is difficult to treat. Many epilepsy patients use cannabis, cannabinoid extracts, or other cannabinoids for symptom relief based on anecdotal accounts, and, more recently, clinical trials of cannabidiol (CBD). Little systematic data has been collected about the naturalistic use of cannabinoids for epilepsy.

Methods. Patients or adult caregivers registered with the Realm of Caring Foundation, a non-profit focused on education related to the use of hemp products for epilepsy and other health conditions, were invited to participate in a web-based survey study that assessed demographic and health-related outcomes. Participants completed a baseline assessment and were then asked to complete follow-up surveys every 3 months. Analyses compared patients using cannabinoids versus those who were not at baseline, and to evaluate changes from baseline among patients who were not using cannabinoids at baseline, but initiated use during the follow-up assessments. T-tests and Chi-Square tests were used and significance was determined at $p<0.05$.

Results. At baseline, 168 patients were using cannabinoids and 105 were contemplating initiating use, but had not yet done so. Products high in cannabidiol (CBD), versus those high in THC, were predominant among those who had initiated cannabinoid use. On average, cannabinoid users were significantly older than non-users (M=24.0, SD=17.3 vs. M=19.0, S.D.=15.6, p=.02), but users and non-users did not differ on gender, race/ethnicity, or educational attainment variables. Cannabinoid users reported significantly better health satisfaction and sleep quality, and lower anxiety and depression compared with non-users on validated assessments. Non-users were more likely to report past month outpatient hospital, inpatient hospital, or emergency room visits, and were more likely to have had a sick day from work/school in the past month compared with cannabinoid users. There were no differences between groups on quality of life or number of prescription or OTC medications used.

Of the 105 patients not using cannabinoids at baseline, 35 initiated use prior to completing a follow-up assessment. Compared with baseline, the individuals who initiated cannabinoid use had improved self-reported health satisfaction, reduced the number of prescription medications taken, and reduced depression after initiating cannabinoid use. Children in this cohort also had improved sleep following initiation of cannabis or cannabinoid products. One patient stopped use of cannabinoids due to an increase in seizure activity observed after initiating use.

Conclusions. In a convenience sample of epilepsy patients enrolled in an observational research registry, current users of cannabinoids reported better outcomes across a number of health-related measures compared with a demographically similar group of epilepsy patients not using cannabinoids. Among non-users at baseline, initiation of use was associated with improvements in health and a reduction in prescription medications used. This prospective natural history study indicates an overall clinical benefit of cannabinoid use among epilepsy patients using products high in cannabidiol, indicating the need for additional drug development and controlled clinical research in this area.

TREATMENT OF ADULT PATIENTS WITH TOURETTE SYNDROM USING THE NEW MONOACYLGLYCEROL LIPASE (MGLL) INHIBITOR ABX-1431 HCI : A RANDOMIZED, PLACEBO-CONTROLLED, SINGLE-DOSE CROSSOVER STUDY

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Tourette syndrome (TS) is a chronic neuro-psychiatric disorder characterized by the presence of both motor and vocal tics. The majority of patients, in addition, suffers from different psychiatric comorbidities such as obsessive-compulsive disorder (OCB), attention deficit hyperactivity disorder (ADHD), depression, sleeping disorder impulsivity, and anxiety disorder.

In 1988 it has been suggested for the first time that use of smoked marijuana might be effective in the treatment of both tics and behavioural symptoms in patients with TS. Recent open-label and small controlled studies provided some evidence that different cannabis-based medicines including dronabinol, nabiximols and medicinal cannabis are indeed effective and well-tolerated in these patients. Based on this preliminary clinical data, it has been suggested that TS might be caused by a dysfunction in the endocannabinoid system (ECS). Accordingly, it has been speculated that tics can be improved not only by exocannabinoids, but also by an inhibition of the endocannabinoid (eCB) degrading enzymes.

Today the best characterized endogenous ligands of the cannabinoid (CB) receptors are anandamide (AEA) and 2-arachidonoylglycerol (2-AG). The levels of AEA and 2-AG are regulated by the catabolic enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MGLL), respectively. MGLL is the primary metabolic enzyme responsible for hydrolyzing 2-AG in the nervous system.

The new drug ABX-1431 is a potent and selective, orally available irreversible inhibitor of MGLL elevating brain 2-AG levels >10-fold. In contrast to the effects of exocannabinoids such as dronabinol and cannabis, the MGLL inhibitor ABX-1431 acts preferentially on synapses with high neurotransmitter flux due to different receptor engagement extent, kinetics and selective engagement of subsets of brain CB1 and CB2 receptors. Therefore, it can be speculated that ABX-1431 causes less side effects than exocannabinoids.

Here we report the design and preliminary results of the first randomized, placebo-controlled, single-dose, crossover study using ABX-1431 in N=20 patients with TS (https://clinicaltrials.gov/ct2/show/NCT03058562).

THE EFFECT OF LIGHT SPECTRUM ON CANNABIS SATIVA MORPHOLOGY AND CANNABINOID CONTENT

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Cannabis sativa flowers is the main source of Δ-9-tetrahydrocannabinol (THC) used as galenic drug. To produce standardized product is necessary to control properly environmental factors (Latta and Eaton 1975), and for this reasons indoor cultivation of plants is recommended. One of the most important growing factor of cannabis is light and its spectrum has to be optimized to affect the cannabinoid yield. Short wavelength irradiation is the object of our study because (UV-A and UV-B) often produce high content of secondary metabolites. In two independent trials a panel of 11 different type of lamps have been compared when they are used to grow *Cannabis sativa*.

Method: Cloned plants of a THC prevalent strain named G-170 have been grown inside grow box of 1.20 x 1.20 x 2.00 m high. Each box was equipped with one type of lamp. The cuttings are transplanted into pots of ~12-15 cm in diameter, grown at temperature of ~ 25°C and humidity lowered ~70% RH. Nutrient solution has pH 5,9 and EC = 2 mS/cm, using fertilizers for Cannabis plant needs. When plants were large enough, n° 9 clones were selected for uniformity and flowering was induced by shortening the photoperiod to 12/12 hours (light/dark).During this phase the PPFD applied in all the boxes was quite the same for all the tested light conditions (~400-600 µmol/m^2/s). Harvest was done once, after about 46 days of flowering phase. Flower yield and cannabinoid concentration were the principal parameters tested.

Results: The three LED lamps tested could represent an improving, similar and a lower alternative to the HPS or ~~plasma~~ other innovative lamps. The flower yield obtained with high efficiency LED produced 53 gr/plant and more than 7 gr/plant of cannabinoids, while the HPS were at a significant level less performing. The highest concentration of cannabinoids (%) in flower was obtained with NS1 bars lamp produced by Valoya.

Conclusions: Our results suggest that LED lamps are very efficient already superior to traditional lamps like High Pressure Sodium (HPS). Many condition has to considered: distance between lamp and plant, light uniformity, warming of the environment and the most important parameter the energy consumption that means cost of the final pharmaceutical product. The fast spreading and preference of LED lamp in Cannabis plans will be lowered the cost of these type of lamps and substitution of HPS will be a close requirement to obtain an efficient method of Cannabis production. Economic study is need to summarize the huge amount of data collected and to identify the rank of the parameters that could be considered by the point of view of efficient and suitable productive strategy as botanical raw material or cannabis extract.

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TERPENES AND TERPENOIDS IN CANNABIS

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Thesis: Data science can allow doctors to prescribe specific strains of cannabis to patients based on their medical condition.

Cannabis is a being used to treat a wide variety of disorders with increasing acceptance. Many users and doctors are aware that strains and varieties of cannabis have different efficacy in treating different disorders, but the science is poorly understood. Cannabidiol and tetrahydrocannabinol, and other variations in cannabinoid content account for some of this phenomenon, but isolated cannabinoids lack the efficacy of "whole plant" cannabis. This phenomenon can be described in part by the psychoactive and medical effects of terpenes present in cannabis, which vary widely from one strain to the next.

Methods: 958 unique cannabis flower samples were analyzed for the concentration of 20 terpenes. The samples are from the state of medical program in Nevada and Massachusetts and were analyzed by accredited local analytical laboratories for legal compliance with state law. This data was analyzed for prevalence, and the ten highest concentration terpenes were analyzed for medical properties using a database of peer-reviewed medical papers addressing cannabis, cannabinoids, or terpenes (n=258). These same ten terpenes were then illustrated for relative concentration in the 14 most popular strains of cannabis analyzed.

Results: **1)** The 10 most relevant terpenes in the sample set (n=958) where the following: a-pinene, b-pinene, caryophyllene, d-terpinene, humulene, limonene, linalool, myrcene, nerolidol, ocimene. **2)** The results of the above ten terpenes queried for medical benefits in the medical paper database (n=258) is summarized in the following chart:

	Total	Cancer	Anxiety	Depression	Pain	Insomnia	Infection
Pinenes	10	1	5	3	2	2	4
Myrcene	8	1	5	2	2	1	4
Ocimene	6	0	1	1	0	2	2
Limonene	20	6	10	2	3	1	6
d-Terpinene	6	2	0	0	1	0	2
Linalool	13	2	6	5	4	0	3
Caryophyllene	18	2	4	4	4	0	5
Humulene	5	3	1	1	0	0	1
Nerolidol	5	3	1	1	1	0	2

3) The following strains of cannabis were used to illustrate the relative terpene concentration for the ten terpenes surveyed, showing rather consistent ratios between replicate batches of cannabis flower: Juicy Fruit (n=13), Blue Dream (n=11), Bubba Kush (n=9), Sequoia Strawberry (n=8), Acapulco Gold (n=8), Tangerine Power (n=7), Blue Power (n=7), San Fernando Valley OG (n=7), Grand Daddy Purple (n=5), Cheese (n=6), Chem '91 (n=5), Cherry Diesel (n=5), Northern Lights (n=4), Platinum Blue Dream (n=4)

CANNABINOID ANTAGONISTS INDUCE CONVULSIVE SEIZURES; DO THEY ALSO AFFECT COGNITION?

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Introduction: Chronic treatment with the CB1 antagonist rimonabant induces convulsive seizures, as we have shown previously[1]. In the present study we show that such seizures are also elicited by another CB1 antagonist, SLV326. In addition to seizures, effects of CB1 antagonists on cognition have been described. Theta rhythm in the EEG is shown to be a marker of complex behavior, and gamma rhythm is typically associated with cognitive functions. Although CB1 agonists have been described to alter the EEG frequency spectrum, no such data have been described for antagonists.

Methods: In a regulatory repeat-dose toxicity study, Wistar rats were daily dosed with the CB1 receptor antagonist SLV326 during 5 months. In selected SLV326-treated and control animals, EEG and behavior were monitored for 24 hours. Subsequently, random segments of the interictal EEG were selected, totaling 20 minutes per animal. These segments were assigned to subsets of 'active state' or 'passive state', based on Passive Infrared (PIR) motion detection. Spectral information was calculated using a Fast Fourier Transformation analysis.

Results: 25% of SLV326-treated animals showed generalized convulsive seizures, which were EEG-confirmed. Controls were seizure-free. The behavioral signs of the seizures were typical for a limbic origin. The frequency spectrum of the interictal EEG of the treated rats showed a lower theta peak frequency, 6.3 Hz versus 7.2 Hz, as well as lower relative gamma power compared to the controls, 9.45% vs 16.8%. These changes were state-dependent: they were only found during activity. However, the treatment did not affect the amount of activity itself.

Conclusion: Apart from confirming our previous finding that blocking the endocannabinoid system can provoke limbic seizures in healthy rats, this study shows that SLV326 alters the frequency spectrum of the EEG, but only when rats are highly active. It is therefore likely that the EEG effects caused by SLV326 are linked to complex behavior and cognition, which might be present predominantly during active wakefulness.

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REVEALING MASTER REGULATORS OF THE APOPTOTIC PROCESSES TRIGGERED BY CONNABIDIOL IN GLIOMA STEM CELLS

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Glioblastoma is the most common primary brain tumor in adults and resistant to therapy causing tumor recurrence, which is ultimately fatal in 90% of the patients 5 years after initial diagnosis. Cannabidiol (CBD) is a non-toxic and non-psychoactive cannabinoid that has been shown to have antitumor activity in multiple cancer types. Activation of CB1 and CB2 receptors has been previously shown to lead to the inhibition of tumor progression. In this study, we analyzed data of the researchers investigated mechanisms underlying glioma stem cells response and resistance to CBD (*Singer et al., Cell Death and Disease. 2015; 6, e1601; doi:10.1038/cddis.2014.566*). We used an approach that allows a causal analysis of transcriptomics (microarray) data with the help of an "upstream analysis" strategy. The goal of this approach is to identify master regulators in gene regulatory networks in order to understand the main players of the cellular response to the drug treatment and to reveal potential biomarkers of the antitumor effect of the drugs.

Methods: The data analysis strategy includes a state-of-the-art promoter analysis for potential transcription factor (TF) binding sites using the TRANSFAC® database combined with an analysis of the upstream signal transduction pathways (using TRANSPATH® database) that control the activity of these TFs. When applied to genes that are differentially expressed in the cells upon the treatment by the tested compounds, the approach identifies potential key molecules (master regulators) that may exert major control over the change of the expression of these genes.

Results: Limma analysis of the gene expression data with the cut-off of adj.p-value<0.05 reveals 28 up-regulated and 8 down-regulated genes. The GSEA analysis reveals the following biological processes and pathways enriched by the up-regulated and down-regulated genes. Up-regulated GO categories: apoptotic process, angiogenesis, response to organic cyclic compound, cell-matrix adhesion, response to oxidative stress; pathways: TLR5 pathway, p53 pathway, TNF-alpha pathway. The very strongly down-regulated GO terms were: cell cycle, mitotic spindle assembly checkpoint; pathways: E2F network, S phase (Cdk2). Promoter analysis revealed clusters of TF sites in promoters of up-regulated genes for such TFs as C/EBP, E2F, p53 and Nanog. Master regulator search revealed CB1 receptor as the primary activating signal, followed by very strong activation of signaling through such up-regulated master-regulator as SRXN1 (Sulfiredoxin 1) and TXNRD1 (thioredoxin reductase 1) – enzymes and regulatory proteins involved in regulation of oxidative stress; E3 ubiquitin-protein ligase NEDD4 and AMPK-related protein kinase 5 (ARK5) - important markers of tumor malignancy and invasiveness.

Conclusions: We conclude from these findings, that treatment by CBD triggers important anti-cancer mechanisms in the tumor cells that involved regulation of oxidative stress, apoptosis and cell cycle progression. The results of this analysis helped us to better understand signaling mechanisms involved. Such an approach promises to be very effective for rapid and accurate identification of cancer drug targets with true potential. The upstream analysis approach is implemented as an automatic workflow in the geneXplain platform (www.genexplain.com) using the open source BioUML framework (www.biouml.org).

CANNABIS ANALYTICS: A CHEMOTYPE-BASED LABELING SYSTEM

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Introduction: Plants of the Cannabis sp contain hundreds of chemicals in the terpenoid class that have been shown experimentally to possess medicinal properties independently, as well as well as collectively. It is known that terpenoid concentrations account for the variation in taste and odor of different cannabis cultivars, and theorized that this extends to variation in medicinal properties between cultivars as well. A batch of Cannabis sold in a dispensary in the US can have as many as 50 data points describing its terpenoid content. This amount of data can be overwhelming to doctors and patients alike, and can make the process of prescribing or choosing a particular strain difficult. Indeed, that task is usually given to dispensary employees and currently lacks a standard quantitative basis. We theorize that this task can be achieved by reducing terpenoid data using standard machine learning techniques while preserving important variations, and represented in a way that is absorbable to those not familiar with the biological actions of each individual chemical component.

Methods: 470 unique cannabis flower samples from state-approved sources were analyzed for the concentration of 20 terpenes using GC/MS with headspace sampling and 15 cannabinoids by LC/UV over the period of 2 years. This data was then analyzed using Principal Component Analysis for better visualizations and to reduce the 35 data points to 4. These components are then normalized and represented as a series of concentric circles of varying color and size.

Results: Our data methods were able to reduce 35 components to 4 principal components while retaining >70% variation. Each sample can then be reduced using this training set to 4 PC's and represented visually using our system of concentric circles, each representing one PC, with radii that vary according to the absolute value of the PC and a color determined by the sign (+ or -). Samples clustered together in the abstract PC space display similar labels, proving that the system can be used as a means of easily identifying and grouping chemovars.

Conclusion: Our methods were successful in providing a new way to study and categorize chemovars that doesn't require genetic information. While this is a helpful tool to doctors, dispensaries, and end-users, the PC's remain abstract. Future studies will focus on adjusting the axes and using artificial neural networks to connect chemical profile data to human physiological effects using a number of different biomarkers, including heart-rate variability.

PHARMACOLOGICAL IDENTIFICATION OF IQM311 AS AN ALLOSTERIC MODULATOR OF THE CANNABINOID CB2 RECEPTOR

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Because cannabinoid receptor-mediated signaling systems are involved in regulating a multitude of physiological and pathophysiological processes, it is not surprising that the therapeutic cannabinoid field benefited from the early identification of potent and efficacious orthosteric agonists and antagonists. However, the therapeutic use of direct CB_1 cannabinoid receptor agonists is limited due to psychoactive side effects associated with their action in the brain, whereas chronic use of CB_2 cannabinoid receptor agonists could generate immunosuppression and adverse pro-inflammatory effects. Consequently, substantial efforts have been put into seeking alternative ways of modulating cannabinoid receptor activity over recent years, including the targeting of topographically distinct allosteric sites. Negative (e.g. ORG27569 and PSNCBAM-1) and, more recently, positive allosteric modulators (e.g. GAT211) of the CB_1 cannabinoid receptor have been discovered. However, very few CB_2 receptor allosteric modulators have been reported so far. Here we present evidence that IQM311, a compound that was originally developed as a CB_1 cannabinoid and μ opioid receptor orthosteric ligand[1], is a novel CB_2 allosteric modulator.

Methods: IQM311 was investigated as a possible CB_2 allosteric modulator using [^{3}H]-CP55940 and [^{35}S]-GTPγS binding assays performed with membranes of Chinese hamster ovary (CHO) cells stably transfected with human CB_2 or CB_1 cannabinoid receptors (CP55940 is a potent and efficacious orthosteric CB_1 and CB_2 agonist). CB_2 dissociation kinetics experiments with [^{3}H]-CP55940 (0.7 nM), in the presence of IQM311 (1 μM) or of its vehicle, were also performed.

Results: i) IQM311 behaved as a CB_1 agonist at 10 nM but as a CB_1 inverse agonist at 10 μM. ii) It is also a low-potency inhibitor of [^{3}H]-CP55940 binding to the CB_1 receptor ($K_i = 0.81$ μM) and CB_2 receptor ($K_i = 4.6$ μM). iii) At 1 μM, IQM311 significantly enhanced the efficacy with which CP55940 activated CB_2 receptors. iv) The dissociation rate of [^{3}H]-CP55940 from CB_2 receptors was not affected by IQM311 at 1 μM. v) IQM311 behaved as a weak CB_2 inverse agonist at 10 μM, but lacked CB_2 inverse agonist or agonist activity at lower concentrations.

Conclusions: IQM311 enhanced the CB_2 efficacy of the orthosteric agonist, CP55940, and did not induce CB_2 agonism by itself. We conclude that IQM311 is a CB_2 positive allosteric modulator (PAM) that, at higher concentrations, behaves as a CB_2 inverse agonist, and that can also target CB_1 receptors as an agonist and inverse agonist.

(1) Fernández-Fernández et al., *Drug Des. Devel. Ther.* **2014**, 8:263–277.

CANNABIS RECLASSIFIED: REDEFINING 'INDICA' AND 'SATIVA' DRUG TYPES BY GENETICS AND CHEMISTRY

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There is perhaps no debate in the world of Cannabis more contentious than that of species. The genus *Cannabis* has been split into one, two or three separate species, depending on criteria. Outside of the domain of taxonomy, however, 'Indica' and 'Sativa' (as well as 'Hybrid') have taken on other meanings: cannabis breeders and cultivators have adopted the terms as a way of advertising their product's effects, aromas or purported pedigree. The degree to which these labels correspond to their actual ancestry, however, is dubious, and how this informal classification scheme relates to genotype or phenotype has been largely unexplored. In this study, an analysis of 149 cannabis strains was performed, correlating the genotype and chemotype (based on terpene and cannabinoid content of the flowers) to their reported 'ancestry'. We then compared the reported labels to scales we developed by exploiting the genetic and metabolomic data, using the genetic and chemical relationship between individual samples to reclassify each strain.

Methods: 149 cannabis samples, each with a reported ancestry (ranging from 100% Sativa to 100% Indica) from five sources within the Netherlands were genotyped using Genotype-by-Sequencing (GBS), and phenotyped for cannabinoid and terpene content via gas chromatography. The relationship between reported ancestry and genotype/chemotype was compared using principal components analysis (PCA). To derive a corrected classification of each sample using genotype/chemotype, an additive relationship matrix of individual samples based on the genetic and chemical data was used in a mixed-linear model to predict the 'ancestry' of each sample using other samples' labels as a guide.

Results: 1) Samples of different labeled ancestry did not separate well on the primary principal component, making it doubtful that they are based on different species or sub-populations. Similar results were observed using chemotype data. 2) Variation in cannabinoid content was very limited, with few high-CBD types found, and did not correlate to labeled ancestry. 3) Reclassified labels, based on genetic and chemical similarity, respectively, were highly correlated. These reclassified labels also correlated strongly with certain terpenes (Indica with myrcene and sesquiterpene alcohols; Sativa with farnesene and bergamotene), aromas that are popularly associated with these types of cannabis.

Conclusion: The Indica/Sativa classification of Dutch cannabis does not correspond to distinct genetic lineages or to cannabinoid type, but there are genetic and chemical similarities that explain the variation between the groups. Deconvolution of the Indica-Sativa ancestry showed a strong relationship between the chemical and genetic profiles, suggesting that the distinct terpene contents of the types are heritable. It is likely that strains are classified by their distinct aromas, and not their lineages, which has a direct impact on the genetics of this crop.

HIGH PERFORMANCE ENGINEERED CANNABIS POWDERS FOR INHALATION VIA A DRY POWDER INHALER

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Smoking of cannabis is an unattractive option for many patients and exposes the user to a range of potentially toxic agents associated with a botanical product and combustion. Edibles offer an alternative but are slow onset, exhibit poor bioavailability and are often accompanied by gastrointestinal side effects. Propellant-based inhaler formulations typically result in high oropharyngeal deposition, throat irritation and poor delivery efficiency. An ideal approach would be to create dry powders that offer consistent and high lung deposition when administered from a simple device while offering the same rapid onset of activity associated with smoking. To this end, engineered powders containing cannabis or the surrogate, hops-extract, have been spray-dried and performance-tested using a monodose dry powder inhaler.

Methods: Proprietary aqueous emulsion formulations were prepared and dispersed via high-shear mixing (Microfluidics M110P, Westwood, MA). The emulsions were then spray-dried (Mobile Minor, GEA, Columbia, MD) producing micron-sized dry powders with a content of 12 % w/w of active. The powders were sized by laser diffraction (MS3000, Malvern Inst., Malvern, UK) using an integrated dispersion system (AeroS). Thereafter, 10 mg of one powder (lot 0328) was filled into size 3 HPMC capsules (Capsugel, Morristown, NJ) under controlled relative humidity (RH) using a bespoke dosator for subsequent evaluation using the RSO1 single dose capsule inhaler (Plastiape, Osnago, Italy). Delivery performance over 2 months bulk capsule storage at different RH conditions (10 to 40 %) was evaluated using the Alberta Idealized Throat (AIT, Copley Sci., Nottingham, UK) operating at 28.3 L/min with the emitted dose, 'lung dose' and device retained-dose being determined gravimetrically (n = 6). The mass median aerodynamic diameter (MMAD) and fine particle fraction (FPF) was determined using the Andersen Cascade Impactor under similar conditions.

Results: The spray-drying process produced yields of approximate 75%. The powders filled readily into capsules indicating good bulk flow properties. The average volume median diameter (X_{50}) for the powders was 2.4 um and the GSD was 1.9. The emitted dose from the RSO1 device using lot 0328 was 85.6 ± 2.4 % with 8.2 ± 3.4 % deposition in the 'throat' and a 'lung delivery' of 77.4 ± 2.3 % (n = 6). The MMAD and FPF of the t = 0 powder was 2.7 um and 77 % respectively. The effects of storage time and RH for the emitted dose are summarized in Table 1.

Table 1 Effects of Storage Conditions on Emitted Dose

RH (%) @ ambient	Day 14	Day 28	Day 56
10	88.7 ± 1.5 %	95.4 ± 6.5 %	92.4 ± 1.0 %
20	88.5 ± 2.5 %	91.5 ± 2.8 %	88.7 ± 1.8 %
30	84.6 ± 1.1 %	85.8 ± 1.3 %	84.2 ± 1.2 %
40	83.2 ± 1.3 %	84.2 ± 2.7 %	81.2 ± 1.6 %

Conclusions: Cannabis and surrogate dry powders for inhalation were successfully manufactured via spray-drying. Bench-testing using an established dry powder inhaler device demonstrated that high delivery efficiency could be maintained over a range of storage conditions for at least 2 months with concomitant low throat deposition and high lung delivery.

QUALITY ASSESSMENT OF CBD RICH CANNABIS EXTRACTS PURCHASED FROM INTERNET

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Introduction: Cannabidiol (CBD) rich preparations are becoming increasingly popular. Many different vendors from all over the world now offer cannabis extracts via internet based shops. As with "classical" medication, assessment of product safety and conformity is an important parameter. The goal of the present project was to check the quality of 24 cannabis oil preparations purchased via internet in seven European countries.

Methods: The following parameters were analyzed: cannabinoids (CBD, CBDA, THC, THCA, CBG, CBGA, CBN) using HPLC/UV; major terpenes (β-caryophyllene, linalool, α-pinene, β-myrcene, α-humulene, guaiol) using GC/MS, residual solvents using HS/GC/MS; over 200 pesticides using LC/MSMS and GC/MS; metals (Zn, Hg, Pb, Cu, Zn, Sn, Ni, Hg, Cr, Cd, As) using ICP/MS and DMA.

Results: Eight out of the 24 samples had CBD + CBDA concentrations within 10% of indicated values; ten had concentrations ranging from 75 - 90% of indicated values; five samples had concentrations > 25% inferior to stated values. In one sample, the theoretical CBD concentration was not labelled. All but one sample had THC concentration values < 0.2%.

Sesquiterpenes were generally present in higher concentrations than monoterpenes. β-caryophyllene was present in all samples; ranging from 0.01% to 0.91%. Other terpenes were more often present in non-decarboxylated and CO_2 extracted samples than in decarboxylated samples prepared using solvent extraction.

All metal concentrations were within the legal limits for food supplements in Europe. Residual solvents were detected in two samples using ethanol extraction; 2-propanol was detected in one sample. Propamocarb, a fungicide, was the only pesticide detected. It was present in 3 samples at a concentrations ranging from 1- 2 mg/kg.

Conclusion: The present study allowed accessing the quality of 24 hemp oils from Europe. Cannabinoid concentrations were not always in accordance with producer information. Monoterpenes and sesquiterpenes concentrations varied widely, presumably depending on the sample extraction method. Solvents, metals and pesticides does not seem to be a major problem in hemp oils.

TERPENES PROFILE, FLAVONOIDS FINGERPRINT AND CANNABINOIDS CONTENT OF SEVEN CANNABIS SATIVA FIBRE-TYPE VARIETIES CULTIVATED IN ITALY

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Cannbis sativa L. is well known due to its history pharmacological and social impact. Its use as a psychoactive drug as a folk medicine ingredient and a source of texile fibre has been widespread since ancient times. Fibre-type plants remain at the moment underused in the pharmaceutical ambit where drug-type *C.sativa* is employed as medicinal *Cannabis*. Despite the large number of studies on cannbinoids composition of drug-type plants, scarce researches deal on reliable metabolite profiling of terpenes and flavonoids especially characterising fibre-type chemotypes as well. The aim of the present study was to investigate the cannabinoids, terpenes and flavonoids profile of eight different fibre-type *C.sativa* L. varieties cultivated in Italy by using Solid Phase Microextraction (SPME) coupled to GC-MS and high Resolution Mass Spectrometry (LC-Orbitrap) to analyse bioactive compounds. This could be implementing the current knowledge useful in pharmaceutical and nutraceutical ambits.

Methods: Eight *C. sativa* fibre-type varieties cultivated in Italy were involved in this study (Futura 75, Finola, Fedora, Kompolti, Lipko, Fibranova, Uso 31, Eletta campana.). The samples (100 mg dry material) belonging to different breeding lines were cultivated under the same agronomic conditions. SPME using CAR/PDMS/DVB fiber was used for terpenes analyses while extraction of flavonoids and cannabinoids were performed by using Accelerated Extraction Solvent (ASE) technique.

Results: several differences were obtained among the different varieties in term of terpenes and flavonoids that result more abundant in Fibranova chemotype. This contained large amounts of α-pinene, β-myrcene, camphene and linalool. In term of cannabinoids the CBD and CBDA were detected as major cannabnoids in the ranges of 0.9-3.2 mg g^{-1} and 1.3-46.8 mg g^{-1} respectively. Other minor cannbinoids were also characterised by using high resolution approach as chemotype's markers also.

Conclusions:
As demonstrated by the present study the analytical approach based on Headspace-Solid-Phase Microextraction (HS-SPME) coupled to GC-MS and LC-Orbitrap represents a valid tool for a comprehensive quality study of Cannabis fibre-type varieties that could be also revealed strategic and complementary to some *Cannabis* drug-type chemotype in which THC is present but at low concentration level (<1%).

HS-SPME AND GC-MS FOR THE COMPREHENSIVE STUDY OF TERPENES AND CANNABINOIDS EMITTED FROM MEDICAL CANNABIS SATIVA FLOS DURING VAPORISATION BY USING A MEDICAL DISPOSAL

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Cannabis (*Cannabis sativa L.*) is the most controversial plant ever exploited by mankind and its effectiveness for treating various medical conditions has been well documented. Cannabis administration through tea, oil or vaporisation represents the most common ways to use cannabis for therapeutic purposes. In particular, the vaporisation of cannabinoids by heating plant matter to a temperature where active cannabinoid vapours form but below the point of combustion is considered a safe method of intrapulmonary administration. Terpenes recently have received great attention for their synergic actions with cannabinoids defined as "entourage effect". The present study aim to investigate the cannabinoid's profile and terpene's fingerprint of three medical varieties of *Cannabis sativa* L. Flos. generated during vaporisation with medical disposal. This research aimed to evaluate the compounds administrated during therapy simulating the real use conditions. Therefore a method based on HS-SPME was validated for analysis of both terpenes and cannabinoids into vapour phase of medical disposal.

Method Bedrocan®, Bediol® and Bedica® medical chemotypes are involved in the present study. 100 mg plant materials were subject to different vaporisation temperature (180, 190, 200 and 220 °C) to study the proportion of active compounds generated during vaporisation. For this purpose, a medical disposal Volcano® was used for all experiments.

Results: Bedrocan®, Bediol® and Bedica®, as expected, showed a complex and different profiles in term of terpenes isolated from the vapor phase (up to 100 compounds were identified). β-myrcene, as an example, remains the most abundant terpene isolated into vapor during vaporization of Bedica chemotype. HS-SPME was optimized showing that CAR/PDMS/DVB fiber gave the best results for study of terpenes and PDMS for cannbinoids analysis. 200 °C represents the vaporization temperature to obtain both maximum concentration of THC and CBD and to preserve the terpenes profile of original plant material as possible.

Conclusions:

As evidenced through the present research the analytical approach based on Headspace-Solid-Phase Microextraction (HS-SPME) coupled to GC-MS represents a valid tool for a comprehensive study of Cannabis flos used by means of vaporisation as therapeutic strategy.

Acknowledgments:

LC-HRMS ORBITRAP AND HS-SPME COUPLED WITH GC-MS AS ANALITYCAL APPROACH FOR THE COMPREHENSIVE QUALITY EVALUATION OF MEDICAL CANNABIS SATIVA L. FLOS AND OILS PREPARATIONS

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Cannabis (*Cannabis sativa L.*) is a highly promising medicinal plant with well documented effectiveness and increasing use in the treatment of various medical conditions. Differences between the pharmaceutical properties of different cannabis varieties have also been attributed to strictly interactions, defined as 'entourage effect', between cannabinoids and terpenes as a result of synergic action but scarce information are present in literature. Analytical techniques based on GC-MS and LC-MS like Q-TOFf or Orbitrap represent today the election techniques to investigate the active compounds of cannabis and its derivates due to their precision and sensitivity. The aims of the present study were the investigation of cannabinoid's profile and terpene's fingerprint of two medical varieties of *Cannabis sativa* L. flos. and evaluation of their trend and stability in different oil preparations by using Headspace-Solid-Phase Microextraction (HS-SPME) coupled to GC-MS and Accelerated Solvent Extraction (ASE) coupled to LC-Orbitrap.

Methods: Bedrocan® and Bediol® medical chemotypes are involved in the present study. Three different sample oil's preparation methods were tested and compared in the present study to evaluate different conditions (inflorescence pre-heating and oil heating) and they were monitored for a storage period of 6 weeks at two different temperatures (4 and 25 °C).

Results: Bedrocan® and Bediol® show a complex and different profiles in term of terpenes isolated in the headspaces (up to 100 compounds were identified). HS-SPME was optimized showing that CAR/PDMS/DVB fiber gave the best results. Extraction of cannabinoids from inflorescence was achieved by ASE giving good results in term of recovery and repeatability of the methods (>80% and <5% respectively). Several differences were observed in term of cannbinoids and terpenes extracted by the three different adopted procedures. In particular cannabis oil obtained by using ultrasound apparatus gave the best combination of active form of cannabinoids contained and terpenes that remain stable during storage period particular evident for some terpenes as β-caryophyllene.

Conclusions:

The new recent analytical approach based on Headspace-Solid-Phase Microextraction (HS-SPME) coupled to GC-MS and Accelerated Solvent Extraction (ASE) coupled to High Resolution LC-Orbitrap represents a valid tool for a comprehensive study of *C. sativa* Flos and derivates quality.

EFFECTS OF FULL SPECTRUM CANNABIS CONCENTRATE APPLIED TO MALIGNANT MELANOMA: SINGLE CASE STUDY AND LITERATURE REVIEW

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Orally and topically applied cannabis derived concentrates with measurable amounts of Delta-9 Tetrahydrocannabinol (Δ9-THC) and Cannabidiol (CBD). Interact with the enzyme Fatty Acid Amide Hydrolase (FAAH), the cannabinoid receptors CB1, CB2 and the transient receptor potential vanilloid1 (TRPV1) channels. These actions, of the cannabinoids THC and CBD, present in multiple research studies to have proapoptic and antiangiogenic effects on melanoma cells. CB2 receptors, are distributed throughout the lymphatic system, and are found in the basal epidermal layers of skin. Specifically, melanoma cells are known to upregulate CB1 and CB2 receptors. TRPV1 receptors are present on the dermis and epithelial cells where CB2 overexpresses on the melanoma surface. CBD has shown to be an effective proapoptic phytochemical agent when interacting at the CB2 receptor. CB1 receptors are found in the central and peripheral nervous system, thyroid, pituitary, and adrenal glands. Δ9 - THC works at the CB1 receptor site to inhibit the enzyme Fatty Acid Amide Hydrolase (FAAH). This Δ9 -THC motivated inhibition of FAAH increases the concentration of the endocannabinoid Anandamide (AEA) at the CB1 receptor site. Where, AEA is then degraded with resulting proapoptic effects on melanoma cells. Δ9- THC also shows potential to induce autophagy when interacting at the TRPV1 channel, as a precursor to the proapoptic response to melanoma cells. Both CBD and Δ9-THC are shown to be effective antiangiogenic agents decreasing cellular proliferation, tube formation, and migration.

Methods: 62 y Caucasian Female with a superficial spreading malignant melanoma, Clark Level III, Stage 1A, Breslow depth 0.4 mm on the outer aspect of the R deltoid. 12/12/14 began daily topical application of full spectrum cannabis concentrate oil containing 68% Δ-9 THC and 2.5% CBD, mixed in a carrier of coconut oil. Oral ingestion of the same oil concentrate, 1 capsule every morning from 1/7/15-2/11/15, then stopped for persistent side effect of dizziness and lethargy. Continued topical oil application until 2/12/15.Photo documentary timeline of healing melanoma.

Results: 2.25.15 PET scan testing after 60 days of treatment showed complete resolve of Stage 1A malignant melanoma. 6.21.17 Biopsy- Melanoma IN SITU, margins clear to 1cm.

   12/13/2014   12/25/14   01/4/2015   01/12/2015   01/12/2015   01/26/ 2015
02/15/2015

Conclusion: Topical application of a concentrate of full spectrum plant extract with measurable amounts of both THC and CBD may be an effective first line treatment for malignant melanoma.

CANNABIS OILS BEING USED FOR CHILDHOOD EPILEPSY IN THE AUSTRALIAN COMMUNITY

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Introduction. Recent clinical and preclinical evidence indicates the efficacy of various cannabinoids in seizure reduction. In Australia, there are currently no registered cannabinoid medicines that can be prescribed for the treatment of epilepsy, and official government channels for accessing cannabinoid products are slow and complex. This has driven many families to illegally source cannabis oils and tinctures to manage the seizures of family members. Our recent survey indicates that 13% of Australian families with a child with epilepsy are following this approach (Suraev et al., *Epilepsy and Behavior.* (2017)). Media coverage and anecdotal reports suggests that there is sometimes remarkable efficacy of these oils and tinctures.

Methods. The PELICAN study liaises with families who are currently using cannabinoid preparations to treat their child with epilepsy, as well as those who have previously used and stopped, and those who have never used cannabis to treat their child's epilepsy. A semi-structured interview probes issues around the safety and efficacy of the products being used, reasons for and against trying cannabis, and concerns surrounding disclosure to health professionals. Samples of the cannabis products are collected and analysed for 11 different cannabinoids and 5 different terpenoids using LC-MS/MS. Urine samples taken from the children being treated are also analysed for cannabinoids and their metabolites.

Results. Of the 39 families interviewed to date, 21 were currently using cannabis products, 3 had previously used and stopped, and 15 had never used cannabis to treat their child's epilepsy. Treatment-resistant epilepsy was reported in most families who had tried cannabis products, but in few of the control families that had never used cannabis. A large proportion of currently using families reported beneficial effects of cannabis on their child's condition, with many reporting reduction or cessation of the use of conventional antiepileptic drugs after initiating cannabis.

A total of 37 cannabis products were collected, with some families supplying multiple products that had been used with the same child. A total of 95% (32/37) of products had been locally sourced in Australia. A wide variety of cannabinoid and terpenoid profiles were identified in these products, including THC dominant, THCA/THC combined, CBD only, and THCA/CBDA combined. The total cannabinoid content of samples perceived as "effective" (>50% reduction in seizures) ranged ffrom 1.92 to 146.4 mg/g. Beta-caryophyllene was the most prevalent terpenoid present.

Conclusions. The PELICAN study provides unique insight into the use of illicit artisanal cannabis products for childhood epilepsy in Australia. The high variability of cannabinoid and terpenoid content in different products reported as effective is a particularly striking result. The study is continuing to recruit throughout 2017 in both New South Wales and Queensland.

THE BAN ON CANNABIS IN BELGIUM: IMPLICATIONS FOR MEDICINAL CANNABIS USERS' ACCESS TO CANNABIS

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Introduction: In recent decades the acceptance of medicinal cannabis use increased worldwide. The Belgian legislation on cannabis still prohibits its use, sale and possession. No approval for medicinal use exists, except for MS patients who are allowed to treat their spasms with Sativex. Therefore, the current policy limits the sources of supply that Belgian medicinal cannabis users can rely on for the purchase of their cannabis products. This paper addresses the implications of the ban on cannabis in Belgium for medicinal cannabis users living in Flanders regarding the access of cannabis. Previous research with medicinal cannabis user populations shows that accessibility of cannabis is an issue in countries where cannabis for medicinal use is prohibited (e.g. United Kingdom) (Coomber et al., 2003; Ware et al., 2005) and even sometimes in countries where an official medical cannabis program is installed (e.g. Canada) (Belle-Isle et al., 2014; Belle-Isle & Hathaway, 2007; Aggarwal et al., 2009).

Methods: This paper is based on the qualitative part of a wider study that is designed in order to better understand the experiences and characteristics of medicinal cannabis users living in Flanders. In-depth interviews were conducted with self-reported medicinal cannabis users (N=57). Next to in-depth interviews we conducted an online survey with cross sectional design. The eligibility criteria for respondents are: a minimal age of eighteen and the use of cannabis for health purposes currently or in the past.

Results: A recurring difficulty that came up during the interviews with medicinal cannabis users was the accessibility of cannabis. This paper addresses the different sources of supply Flemish medicinal cannabis users can rely on and the aspects that cause difficulties for obtaining cannabis products, including distance, legal concerns, problems with cultivating cannabis, costs, medical support, health problems and the availability of cannabis products. In addition this paper shows how these obstructions influence their cannabis use patterns, health and daily lives.

Conclusion: Data indicate that medicinal cannabis users in Flanders face multiple problems in their search for cannabis products. Based on their personal narratives it becomes clear that several factors cause these problems and impact the lives of medicinal cannabis users in specific ways. When Belgium continues to prohibit all cannabis products, except for the use of Sativex by MS patients, the access of cannabis remains problematic. If policy debates on regulating cannabis start, these findings can be taken into account together with the existing literature that discusses the aspects that are important for the access of medicinal cannabis.

DIFFERENTIAL MODULATION OF ADDICTION AND PAIN BY CBD AND CBD-DERIVATIVES

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Cannabis contains a unique class of terpenophenolic compounds called cannabinoids and is a natural source of Δ^9- tetrahydrocannabinol (Δ^9-THC) and cannabidiol (CBD), its two major constituents with a tremendous therapeutic potential. These two compounds, however, have very different pharmacological profiles. Since the discovery of its principal psychoactive compound (Δ^9-THC) in 1964, cannabis research, by and large, had been revolving around Δ^9-THC and its derivatives. However, in recent years, cannabidiol (CBD), a non-psychoactive compound in cannabis is drawing a lot of attention due to its therapeutic potential such as anti-inflammatory, analgesic, anti-nausea/anti-emetic, anti-psychotic, anxiolytic and anti-epileptiform, anti-convulsant. In the present work, we address the analgesic activities of CBD and CBD derivative (CBD-Val-HS, NB2111) to treat paint without an abuse liability and also the interaction of these compounds with the opiates.

Methods
Conditioned Place Preference Paradigm was used to assess abuse potential. Nociceptive Assays; hotplate, adnominal writhing and Cisplatin induced Neuropathy (CIN) were used to measure the analgesic/anti-inflammatory activities.

Results
- CBD blocks morphine reward
- CBD-Val-HS (NB2111) blocks oxycodone reward.
- Neither CBD nor CBD-Val-HS (NB2111) showed rewarding or aversive activity.
- CBD-Val-HS (NB2111) + oxycodone retains analgesic effects on clinically-relevant pain assays.
- CBD-Val-HS (NB2111) produces analgesia when given alone across all pain assays.
- NB2111 alone provides better pain coverage than plant-derived CBD when compared to morphine.
- High-dose NB2111 alone provides comparable pain coverage to morphine.
- Lower dose NB2111 when combined with "mini-dose morphine" provides comparable pain coverage to high dose of morphine alone.

Conclusions
We conclude that CBD, and a CBD derivate can block opioid reward while retaining their full analgesic efficacy. More importantly, the CBD derivate (CBD-Val-HS, NB2111) when administered alone shows analgesic activity equivalent to opioids but without any abuse liability. This work suggests a novel non-addictive therapy for use in pain management.

EXPLORING THE ANTITUMOR EFFECTS OF CANNABIS ON CANCER CELLS

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Background

Cannabis plants contain more than 150 distinct phytocannabinoids which are presumed to have bioactive properties. Yet, the identification of *Cannabis* components are usually limited to several major cannabinoid species. Recently, the therapeutic potential of these phytocannabinoids has been rediscovered in cancer research as these compounds were found to have palliative effects in oncology. However, there is also accumulating evidence showing possible phytocannabinoid antitumor effects. In response to phytocannabinoids, several studies showed a regression of different tumor types *in vivo*. Further investigations *in vitro* have revealed that they can induce cell death and inhibit proliferation of cancer cells. The concentrations and combinations of various phytocannabinoids determine both medicinal and adverse side effects in patients. Therefore, analyzing the chemical content of differing *Cannabis* plants is of major importance.

The objective of this research was to assess a variety of *Cannabis* preparations and to elucidate which factors are responsible for their antitumor effects, in order to better understand how *Cannabis* may effectively treat cancer

Methods

We perfected extraction techniques and identified distinct compositions of 13 clinically-used *Cannabis* strains. We then explored the differential antitumor effects of these *Cannabis* extracts (differing in cannabinoid compositions) on 12 cancer cell lines.

Results

Depending on the applied concentrations, results indicated that certain *Cannabis* extracts have statistically different ($p < 0.0001$) effects on cancer cell survival. In addition, differing cancer cell lines vary in sensitivity to various *Cannabis* extracts. For example, treatment with one *Cannabis* extract (4 µg/mL) resulted in cancer cell death ranging from 3% to 36% (LNCaP and PC3 cell lines, respectively). Furthermore, whole *Cannabis* extracts were found to be more potent at lower concentrations (4 µg/mL) in comparison to using pure Δ^9THC (8 µg/mL) to produce the same amount of cell death when applied to specific cancer cell lines.

Conclusions

Categorizing cancer cells according to their response to medicinal *Cannabis* will provide valuable information for the development specific *Cannabis* treatments for subgroups of cancer patients.

WOBE437 IS A POTENT AND SELECTIVE INHIBITOR OF ENDOCANNABINOID CELLULAR REUPTAKE

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The extracellular effects of the endocannabinoids anandamide (AEA) and 2-arachidonoyl glycerol (2-AG) are terminated by enzymatic hydrolysis after crossing cellular membranes by facilitated diffusion. The lack of potent and selective inhibitors for endocannabinoid transport has prevented the molecular characterization of this process, thus hindering its biochemical investigation and pharmacological exploitation. We recently reported the design, chemical synthesis, and biological profiling of natural product-derived N-substituted 2,4-dodecadien amides as a selective endocannabinoid uptake inhibitor (Chicca et al., 2017). The highly potent (IC50 = 10 nM) inhibitor N-(3,4-dimethoxyphenyl)ethyl amide (WOBE437) competitively inhibited AEA and 2-AG uptake in cells. WOBE437 at 0.1-1 microM showed 50% inhibition of AEA uptake as compared to vehicle-control in Neuro2a mouse neuronal cells and primary mouse cortical neurons over a timeframe of 15 min (Chicca et al., 2017). Furthermore, using a ^{14}C-radiolabelled WOBE437 derivative, we could show a saturable binding kinetics in membrane preparations obtained from U937 human monocytic cells and mouse total brain. In both cases, ^{14}C-WOBE437 exhibited a Kd value of 10-15 nM and the binding was competable with the endocannabinoid AEA, noladin ether and the AEA uptake inhibitor OMDM-2 (Chicca et al., 2017). In vivo, WOBE437 exerted pronounced cannabinoid receptor-dependent anxiolytic, antiinflammatory, and analgesic effects in mice by increasing endocannabinoid levels (Chicca et al., 2017).

In this presentation, we describe a suitable inhibitor to target endocannabinoid membrane trafficking and outline the discovery a novel endocannabinoid pharmacology.

Reference:
A. Chicca, et al., Chemical probes to potently and selectively inhibit endocannabinoid cellular reuptake. *Proc. Natl. Acad. Sci. U S A*, (2017), in press

CONTROLLED ENVIRONMENT TECHNOLOGY FOR THE PRODUCTION OF PHARMACEUTICAL GRADE STANDARDIZED CANNIBINOIDS.

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Cannabis plants, like virtually all organic life, are a product of their genetics and the environment in which they grow. The range and diversity of genetic variations available to the emerging medical cannabis industry sector is matched by the equally diverse environments in which this commodity is produced. This makes it very challenging for medical cannabis producers seeking to raise the status of cannabis to that of a conventional pharmaceutical commodity. Both anecdotal and now mounting evidence from clinical trials has found that the variability in the quality of the plant, defined as the content and profile of over 100 compounds including THC and CBD, has a significant influence on the potential efficacy of the medicine.

In the course of our research in the field of biological life support for human space exploration we have developed a number of environment control technologies and horticultural management strategies designed to ensure the survival of human explorers during long term missions to the moon and Mars. These same technologies are now being deployed in service of the initiatives related to standardizing the production and quality of pharmaceutical grade medical cannabis. This technical challenge will be presented in detail as will early results of the application of precision environment control and horticultural management strategies in a cannabis crop.

STANDARDS OF CARE AND CLINICAL OUTCOMES: EMERGING DATA FROM A NATURALISTIC SAMPLE OF THE CANADIAN NATIONAL CANNABIS PROGRAM

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Canada's federally regulated legal access program for cannabis medicines has now existed for over 15 years, and remains in constant legislative evolution (Gov't of Canada, 2001, 2014, 2016). Available cannabis products via Health Canada (HC) include dried *cannabis flora*, and orally ingested cannabis oils or capsules. Federal courts have also provided allowances for Canadians with serious medical conditions to cultivate their own cannabis. We report on a consecutive data-set of 150 patients assessed for cannabis access to treat two broad categories of medical indications: Pain (N=96, M=80.2%, F=19.8%, μ_{age} =42.2) and affective (i.e. mood/anxiety) disorders, (N=54, M=79.6%, F=20.4%, μ_{age}= 37.6).

Methods: Our methodology (Moller et al, IACM 2015, ICRS 2016) employs a standardized electronic questionnaire providing standardized severity self-ratings (5-point Likert Scale) of key symptoms: Pain, Sleep Quality, Mood, Relaxation and Stress Perception, and Composite Wellness Score (CWS, range: 5-25) at baseline intake (t=0) and monitoring each clinic visit for renewal of cannabis authorization in 6 month intervals. To qualify for study inclusion, a minimum duration of 12 treatment months were required, with results reported at 6 month increments. Auxiliary qualitative data was obtained via retrospective chart review.

Results: Cohort score changes over time were as follows for the Pain Group (PG): **PAIN** at t=0|2.1, t=12mos|2.8, t=24mos|2.6; **SLEEP**: t=0|2.0, t=12mos|2.8, t=24mos|2.6; **RELAX**: t=0|2.5, t=12mos|3.3, t=24mos|3.3; **MOOD**: t=0|3.0, t=12mos|3.5, t=24mos|3.4; **STRESS**: t=0|2.3, t=12mos|2.9, t=24mos|2.8. Overall, the global trend was significant improvement over the first year, then a tapering of **CWS** at the 2-year mark for the PG: t=0|12.0, t=12mos|15.2, t=24mos|14.8 while for the MHG, **CWS** continued to significantly improve over recorded time, with t=0|12.0, t=12mos|16.6, t=24mos|18.6. For the MHG symptoms, we noted: **PAIN** at t=0|3.0, t=12mos|3.4, t=24mos|3.6; **SLEEP**: t=0|2.0, t=12mos|3.0, t=24mos|3.5; **RELAX**: t=0|2.3, t=12mos|3.5, t=24mos|3.9; **MOOD**: t=0|2.6, t=12mos|3.5, t=24mos|4.0; **STRESS**: t=0|2.1, t=12mos|3.1, t=24mos|3.6. Compared to the MHG, PG patients were, on average, older ($\mu_{age:}$ PG=42.2+/-13.2, MHG=37.6+/-11.7), more likely to use prescription medications at t=0 ($\mu_{meds\%:}$ PG=77.1, MHG=68.5), more likely to have clinically significant comorbidities ($\mu_{morb\%:}$ PG=72.9, MHG=63.0), lower likelihood of requiring pharmaceutical prescriptions from our clinic ($\mu_{Rx\%:}$ PG=7.3, MHG=14.8), and greater frequency of personally cultivating cannabis under the federal legal framework ($\mu_{grow\%}$ PG=32.3, MHG=16.7). 34.4% of PG compared to 11.1% MHG patients reported a major injury history ($\mu_{acc\%}$ auto/sport/industrial) at t=0 intake. Medically relevant tests (blood, polysomnography, imaging studies) were done more frequently for the MHG ($\mu_{test\%}$ PG=22.9 MHG=22.2), with positive findings necessitating clinical intervention or specialist referral in 72.7% of PG cases and 83.3% for the MHG ($\mu_{meds\%}$) 51% of PG vs. 44% of MHG were seeing at least one other specialist; this was a psychiatrist ($\mu_{psy\%}$) in 4.2% of PG cases and 25.9% of MHG cases. Mean approved maximum daily cannabis dosage (μ_{gram}) for PG was 6.0g+/-2.9 (baseline), 6.7g+/- 3.3 (final); MHG initial 5.5g+/-3.2, final 6.2g+/- 4.0.

Discussion: In this medium-sized Canadian case series study, we noted high baseline morbidity/co-morbidity in patients seeking care of pain and affective disorders, and significant global clinical benefit. Gains during Year One of treatment may the most significant, assuming high standards of patient evaluation/education. Numerous qualitative variables could explain the tapering of initial improvement with Pain vs. Mental Health conditions. Judicious use of diagnostic tests, multi-disciplinary health-care specialist involvement, pharmaceutical augmentation strategies are also relevant in ongoing standards-of-care development in cannabinoid medicine.

CURRENT CLINICAL EXPERIENCE AND NEW CONCEPTS IN CANNABINOIDS TREATMENTS (CASE REPORTS)

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This talk will cover current clinical experiences of treatment with cannabinoids performed in medical center CIIM-plus in Slovenia and center for general practice in Luxembourg. The situation in Slovenia has thus far allowed that medical doctors could prescribe only synthetic THC and CBD, but not the natural forms of cannabinoids or whole plant extracts. Recently there have been legislation changes and cannabis has been rescheduled to the second group of controlled substances. This change is not yet implemented in practice.

Regulation regarding CBD products in Slovenia is unclear. In our center we use CBD rich product with low percentage of THC, which are registered and allowed to use in other European countries (Luxemburg, Germany). In our clinical practice we are successfully using combinations of phytopharmaceutical products with cannabinoids and prescribed pharmaceutical preparations with synthetic cannabinoids, but we expect to see even better results once the natural products will be available with a variety of different cannabinoids particularly THC and CBG.

The current clinical experiences are showing immense potential of these molecules in different medical conditions, especially with products, which are rich with terpenes. It is however evident, that treatment protocols have to be individually adjusted and carefully monitored. Often they are combined with other prescription medicines and therefore require medical doctors supervision.

In presentation we will present interesting case reports from our clinical practice and show our experience in treating different medical conditions with cannabinoids (malignancy, neurological diseases, skin diseases).

We are developing unique international clinical concept where we use mostly non-psychoactive cannabinoids together with conventional treatments and other natural teratments.

Pepcan-12 (RVD-hemopressin) is a CB2 receptor positive allosteric modulator constitutively secreted by adrenals and in liver upon tissue damage

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Pepcan-12 (RVD-hemopressin; RVDPVNFKLLSH) is the most abundant peptide of a family of N-terminally extended endogenous peptide endocannabinoids (pepcans) shown to act as negative allosteric modulators (NAM) of cannabinoid CB1 receptors [1,2]. Noradrenergic neurons have been identified to be a specific site of pepcan production [3]. However, it remains unknown whether pepcans occur in the periphery and interact with peripheral type-2 (CB2) cannabinoid receptors. We show that pepcan-12 acts as a potent (K_i value ~ 50 nM) hCB2 receptor positive allosteric modulator (PAM). It significantly potentiated the effects of CB2 receptor agonists, including the endocannabinoid 2-arachidonoyl glycerol (2-AG), for [35S]GTP$\square$S binding and cAMP inhibition (5-10 fold). In mice, the putative precursor pepcan-23 (SALSDLHAHKLRVDPVNFKLLSH) was identified with pepcan-12 in brain, liver and kidney. Pepcan-12 was increased upon endotoxemia and ischemia reperfusion damage where CB2 receptors play a protective role. The adrenals are a major endocrine site of production/secretion of constitutive pepcan-12, as shown by its marked loss after adrenalectomy. However, upon I/R damage pepcan-12 was increased in the liver (from ~100 pmol/g to ~500 pmol/g) independent of adrenals. The wide occurrence of an endogenous hormone-like CB2 receptor PAM with unexpected opposite allosteric effects on cannabinoid receptors points towards a role in peripheral pathophysiological processes.

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SHORT-TERM EFFICACY OF CBD-ENRICHED HEMP OIL IN GIRLS WITH DYSAUTONOMIC SYNDROME AFTER HUMAN PAPILLOMAVIRUS VACCINATION

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Background: Cannabidiol (CBD)-based treatments for several diseases, including Tourette's syndrome, multiple sclerosis, epilepsy, movement disorders and glaucoma, is achieving significant therapeutic role, and scientific clinical background is continuously evolving.

Objectives: To investigate the short-term effect of CBD-enriched hemp oil for relieving symptoms and improving the life quality (QOL) in young girls with untoward effects (ADRs) after human papillomavirus (HPV) vaccine.

Methods: In this spontaneous anecdotal, retrospective, compassionate, observational, open-label study, 12 females (age 12–24 years) with severe somatoform and dysautonomic syndrome after HPV vaccination were given sublingual CBD-rich hemp oil drops, 25 mg/kg per day supplemented by 2–5 mg/ml CBD once a week until a maximum dose of 150 mg/ml CBD per day was reached over a 3 month period. Patients' quality of life was evaluated using the medical outcome short-form health survey questionnaire (SF-36).

Results: Two patients dropped out due to iatrogenic adverse event and other two patients stopped early the treatment due to the absence of any improvement. SF-36 detected significant benefits in the physical component score ($P < 0.02$), vitality ($P < 0.03$) and social role functioning ($P < 0.02$) after the treatment. The administration of hemp oil also significantly reduced the body pain according to the SF-36 assessment.

No significant differences from the beginning of the treatment until several months post-treatment were detected in role limitations due to emotional reactions ($P = 0.02$).

Conclusions: This study showed the safety and tolerability of CBD-rich hemp oil and the primary efficacy endpoint. Randomized controlled trials are warranted to characterize the safety profile and significant efficacy of this compound.

KEY WORDS: hemp oil, cannabidiol (CBD), adverse event, vaccine, human papillomavirus (HPV)

TREATMENT OF TOURETTE SYNDROME WITH CANNABINOIDS: FROM CASE REPORTS TO RANDOMIZED CONTROLLED TRIALS

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Introduction: In 1988 and 1993, it has been suggested for the first time that use of smoked marijuana might be effective in the treatment of tics and behavioural symptoms in three and one patient with Tourette syndrome (TS). Five years later, in 1998, results from a survey have been published reporting about 17 patients, who had used marijuana. Of these, 14 (82%) patients experienced improvements of both tics and psychiatric comorbidities including obsessive-compulsive behaviour (OCB) and attention deficit hyperactivity disorder (ADHD). During the following years, further case studies have been published reporting about marked improvements when using dronabinol, nabiximols or cannabis.

Methods/Results: Until today, only two small controlled trials (including N=12 and N=24 patients, respectively) have been performed investigating the effect of orally administered dronabinol in TS. However, both studies demonstrated a significant improvement of tics when using both self and examiner assessments. When using neuropsychological tests, no detrimental effects of dronabinol could be detected on memory, recognition, learning, intelligence, vigilance, reaction time, and attention. No serious adverse events occurred.

Conclusion: In a recent meta-analysis, these promising results lead to the conclusion that there is "low-quality evidence suggesting that cannabinoids are associated with improvements in TS." Based on this data, further studies have been initiated or are in preparation investigating the effects of exocannabinoids such as nabiximols (https://clinicaltrials.gov/ct2/show/NCT03087201), dronabinol plus palmitoylethanolamide (PEA) – in order to investigate, whether in TS this combination is superior to pure dronabinol due to the entourage effect associated with PEA – and medicinal cannabis as well as the efficacy and safety of ABX-1431 (https://clinicaltrials.gov/ct2/show/NCT03058562). ABX-1431 is a potent and selective, orally available irreversible inhibitor of monoacylglycerol lipase (MGLL). MGLL is the primary metabolic enzyme responsible for hydrolyzing 2-AG in the nervous system and therefore regulates the activity of the endogenous cannabinoid system. We therefore expect that in the near future results from a number of well-designed controlled studies will be available investigating the effects of several different cannabinoid agonist drugs in TS. This may open promising new treatment strategies in this complex and chronic neuro-psychiatric disorder.

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