Medical Cannabis and Cannabinoids

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Abstracts

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The abstracts included in these proceedings were pre-reviewed by Rudolf Brenneisen, conference co-chair, and finally reviewed and selected for poster and oral presentations by all SC members.

The SC has no conflicts of interest in connection with the congress and the selection of abstracts.

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Medical Cannabis and Cannabinoids

Abstracts

Abstracts of Poster Presentations

P-1

Cannabis in dentistry? An overview at its historical use and potential future applications

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Introduction: Cannabis has a historical role for pharmacological analgesia/anaesthesia, as well as for dental anxiety. Fast-forward to today's scientific literature, there are many considerations regarding the role of cannabis in dentistry. We examine the role of the endocannabinoid system and its modulation from the dental perspective. Whilst cannabis smoking has been associated with poor dental health, and tetrahydrocannabinol (THC) intoxication can result in tachycardia and acute hypertension, (which could cause drug-drug interaction with sedation and anaesthesia), some cannabinoids seem to be useful for a promising therapy for a range of different conditions of the oral cavity, such as peri-operative analgesia, several neurologic orofacial disorders, like burning mouth syndrome, or even dental anxiety and mouth inflammations. **Aims:** The aim of this study is to review the potential for applications of cannabis-based medications for the dental clinic as well as the risks for the oral cavity associated with cannabis consumption. **Methods:** Literature searches were conducted in MEDLINE/PubMed, Cochrane Central Register of Controlled Trials and Google Scholar from inception to February 2022. Study selection, data extraction, and quality assessment were conducted for references on cannabis in dentistry and endocannabinoid system in the oral cavity. **Results:** As a substantial proportion of adolescents and young adults are exposed to opioids through dental clinicians, it is important to consider that cannabis has also been proposed as a valuable tool for management of the «opioid epidemic», as it does not share the fatal risks such as respiratory depression associated with opioids, whilst providing many of the desired pain-relieving and sedative effects. Cannabinoid receptors not only mediate immunologic as well as pain signals, but are also expressed in periodontal and gingival tissues, as well as in both osteoblast and osteoclasts, making them potential targets for a number of new technologies: from implantology to anti-plaque mouthwashes. See Table 1 for some of the most researched potential uses. **Keywords:** Cannabis, dentistry, pain, periodontal, CBD.
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Table 1. Summary of the most promising potential uses of cannabinoids in dentistry

Condition	Cannabinoids	Method of administration	Reference
Post-operative pain	THC/CBD	• Oral (capsules) • Inhalation (vaporisation)	[1] [2,3]
Temporomandibular pain	CBD	• Transdermal (patch)	[4]
Burning Mouth Syndrome	THC/CBD	• Sublingual (oil)	[5]
Dental anxiety	CBD	• Oral (capsules) • Sublingual (oil)	[6] [7]
Dental Plaque	CBD/CBG	• Transdermal/sublingual (mouthwash)	[8] [9]

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P-2

Cannabidiol exposure modulates the BDNF system in the rat cortico-striatal circuitry

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Introduction: Cannabidiol (CBD) is one of the most abundant phytocannabinoid contained in *Cannabis sativa* L., with a broad-spectrum pharmacological activity. Because of its ability to counteract the psychoactive Δ9-tetrahydrocannabinol (THC), CBD is considered a valuable potential treatment for several psychiatric disorders. **Aims:** Our aims were to evaluate (1) CBD brain distribution and (2) CBD modulatory effects on the brain-derived neurotrophic factor (BDNF), a neurotrophin critical for synaptic plasticity, focusing our attention on the cortico-striatal pathway. **Methods:** For these purposes, we performed a dose-response treatment with CBD by exposing male adult rats to single and repeated CBD treatments at 5, 15 and 30 mg/kg, to investigate both the rapid modulation of BDNF after acute treatment, as well as a potential drug-free time point following 7 days of treatment. **Results:** We show here, for the first time, that CBD can be found in the rat brain, specifically in the medial prefrontal cortex (mPFC), depicting a clear dose-response profile. From a molecular standpoint, we found that a single dose, but not repeated, of CBD (30 mg/kg) is sufficient to upregulate BDNF exon IV, the most abundant BDNF gene isoform, which is paralleled by a similar increase in cortical mBDNF and TrkB. Conversely, the repeated exposure increased BDNF only in the striatum, with a slight decrease in the mPFC, potentially supporting an increased anterograde trafficking of BDNF from the mPFC to the striatum. **Conclusions:** These findings reveal that CBD can be detected in the plasma and in the mPFC, following single or repeated injections, with a specific dose-response profile. Moreover, CBD induced a dose-dependent and anatomically specific modulation of BDNF, which may be functionally relevant and may represent an adding value for CBD therapeutic role. **Keywords:** Cannabidiol, prefrontal cortex, striatum, BDNF. **Acknowledgements:** This study was supported by Curaleaf International and Fondazione Zardi Gori (fellowship to FM).

P-3

Effect of Cannabis sativa chemotype II extract on human mesenchymal stem cells regenerative potential

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Introduction: A growing body of evidence supports using Cannabis to alleviate symptoms or treat several pathologies. However, much of the evidence comes from the study of synthetic or purified cannabinoids, underestimating the role of other components of the Cannabis sativa L. extracts. In this way, other studies show higher efficacy in the therapeutic effects of complete extracts due to the synergy. Under physiological conditions, mesenchymal stem cells (MSCs) orchestrate the regenerative microenvironment to promote tissue regeneration and wound healing. Nevertheless, using MSCs for therapeutic applications is still facing several challenges; research on the potential impact of *C. sativa* extracts on MSC's properties can boost their use in regenerative medicine. **Aims:** This study aims to evaluate the regenerative properties of human MSCs derived from the umbilical cord under the influence of the full spectrum chemotype II of *C. sativa* extracts and elucidate the mechanism underlying these effects. **Methods:** To this end, oil-based extracts (3% w/v) from inflorescences of a chemotype II of *C. sativa* were obtained. MSCs were treated in the presence or absence of 150, 450, and 900 ng/mL *C. sativa* extract. Cell viability, proliferation, migration, apoptosis, and signaling pathways were evaluated. The phenotype of the MSCs was confirmed by flow cytometry. **Results:** The two concentrations of the *C. sativa* extract evaluated (150 and 450 ng/mL) increase MSCs cell migration and inhibit apoptosis induced by oxidative stress (H_2O_2) and staurosporine evaluated by Caspase activation and cleavage. Given the relevance of receptor tyrosine kinase-mediated signaling in proliferation responses and angiogenesis, we evaluated the activation of the PDGFR pathway. The higher dose evaluated of the extract induced the activation of pPDGFRA and pSTAT3 proliferation and immunomodulatory signaling pathways. Interestingly, the conditioned medium of cannabis-primed MSCs also increased the phosphorylation levels of pPDGFRA, pSTAT3, pAkt, and pErk of MSCs, indicating that a paracrine modulatory program was activated on MSCs. **Conclusions:** Despite the need for further research, our findings highlight the ability of Chemotype II of *C. sativa* extracts to enhance the regenerative potential of human MSCs. These findings open a novel therapeutic approach in regenerative medicine. **Keywords:** Cannabis sativa L., mesenchymal stem cells, regenerative medicine.

P-4

Cannabidiol reverses the microglia, parvalbumin cells, and perineuronal nets changes in a rodent model of schizophrenia

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Introduction: Repeated treatment with glutamate NMDA receptor antagonists such as MK-801 produces behavioral and cellular changes associated with schizophrenia. In previous studies, we observed that cannabidiol (CBD) could prevent and reverse the memory and social interaction impairments caused by this treatment through mechanisms involving 5HT1A or CB2 receptors [1, 2]. **Aims:** To verify if CBD could also reverse the cellular changes caused by repeated NMDA receptor antagonism. **Methods:** Male C57BL/6J mice were chronically treated with MK-801 (0.5 mg/kg i.p. twice a day for 14 days). One day after the last administration of this drug, the animals began the CBD treatment (30 mg/kg/kg i.p. daily for 7 days). Additional groups received a 5HT1A (WAY100635, 0.1 mg/kg) or CB2 (AM630 0.1 mg/kg) receptor antagonist before each CBD daily injection. Two days later the animals were tested in the novel object recognition (NOR) test and then sacrificed for the immunohistochemistry analysis using Iba-1 (microglia marker) or parvalbumin (PV+) antibodies, or the Wisteria Floribunda agglutinin (WFA, perineuronal nets marker) reaction. **Results:** We confirmed previous results showing that CBD reverses NOR impairments caused by MK-801. At a cellular level, CBD attenuated the decrease in the number of PV+ cells and the intensity of WFA labeling co-localized with PV+ (WFA/PV+) in the pre-limbic cortex, CA1 ventral area, and ventral subiculum of the hippocampus. The 5HT1A and CB2 antagonists prevented CBD effects in the ventral hippocampus but not in the pre-limbic cortex. MK-801 treatment also increased the number of activated microglia in these regions. CBD reserved this effect via 5HT1A and CB2 mechanisms. **Conclusions:** These results corroborate the proposal that CBD possesses antipsychotic effects. They also indicate possible cellular and pharmacological mechanisms involved in these effects. **Keywords:** Cannabidiol, MK-801, PNNs, parvalbumin, microglia. **Acknowledgments:** This research was supported by grants from CAPES, CNPq, and FAPESP (2017/24304-0).

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P-5

Precision therapeutics are here

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Introduction: Genetics may influence experience with cannabis and CBD. With increased access to legal cannabis and the research community expanding their focus on the medicinal uses of cannabinoids, more and more consumers are seeking cannabis for health and wellness. However, cannabinoids and terpenes are extremely complex and research tells us that users can have vastly different physiological responses to individual strains/chemovars or products. This makes it almost impossible to find a perfectly aligned product through trial and error. The truth is, cannabis is personal, and uncovering true endocompatibility for each individual user can be scientifically validated. Combining genomics with biomarkers and measurable outcomes allows us to develop better predictive inferences. There are statistics of adverse events with delta-9-THC consumption and drug to drug interaction resulting in vomiting and abdominal pain [1]. There is an association with frequent emergency visits for treatment and diagnosis, with high diagnostic expense ($30-90K) and general resistance to treatment with anti-emetics and analgesics. Personalized precision therapeutics can be used to support in mitigation of these adverse events looking at Single Nucleotide Polymorphism (SNPs) along with Pharmacogenomics (PGx) for drug to drug interaction and Pharmacokinetics for dosing based on metabolic function. **Aims:** Discuss (1) how EndoDNA is using phytocanabinoids and therapeutics to align with your DNA and Biometrics; (2) the breakthrough scientific approach Endocanna Health has taken to solving for an individualized response to cannabinoids; (3) the latest research and scientific evidence to evaluate and confidently use cannabinoid therapeutics for individually defined optimal outcomes. Explain the scientifically based, genetically focused resource that consistently and reliably matches individuals with the most compatible cannabinoid products. Review specific clinical applications this method is being used in (Phase 2 Clinical Trial). **Methods:** A health profile is used along with a buccal swab EndoDNA test to identify genetic patterns in the cohort of significant relevance. In addition, care councilors received protocol efficacy feedback as well as the use of a biometric device. **Results:** Findings include mutations in genes coding COMT (p=0.0009), TRPV1 (p=0.021), CYP2C9 (p=0.0414), DRD2 (p=0.027) and ABCA1 (p=0.008) were clustered and analyzed to identify a genetic pattern for this specific adverse event. COMT – COMT (catechol-o-methyltransferase) is best known for its association with dopamine levels and processing. Studies have shown an association between mutations of the COMT gene and depression, ADHD & OCD. Dopamine imbalances caused by variations in COMT may influence the processing of THC resulting in a higher rate of CHS [2]. TRPV1 – TRPV1 regulates receptors which respond to heat, ethanol, low pH and are known to interest with CBD and other compounds present in cannabis. TRPV1 has been linked to anxiety and pain responses. Mutations in TRPV1 may be responsible for the hot bathing behavior and abdominal pain present in CHS [3]. ABCA1 – ABCA1 regulates a protein which affects cholesterol and phospholipid levels. Some studies have shown that ABCB1 may alter alter drug pharmacokinetics, and increased cannabis dependency [4]. CYP2C9 – CYP2C9 is associated with the metabolism of many

pharmaceuticals and is one the primary metabolizer of THC. Variations in the CYP2C9 may result in an altered metabolization of THC, resulting in a higher rate of CHS [5]. CYP2C19 – CYP2C19 is associated with the metabolism of many pharmaceuticals and is an accessory metabolizer of THC. Variations in the CYP2C19 may result in an altered metabolization of THC, resulting in a higher rate of CHS [6]. DRD2 - DRD2 is associated with dopamine levels, a neurotransmitter which, in simple terms, controls our brain's reward system. Due to this, dopamine plays a primary role in addiction, fear memory, depression and anxiety. In the past, drugs which target these transmitters often have an effect on the digestive system. The excessive cannabis consumption and nausea associated with CHS may be explainable by mutations in DRD2 [7]. **Conclusion:** This is the largest observational study ever conducted on phytocannabinoid effects correlating with a genotyping method. A peer reviewed approved study was published as a partial example of study findings. Western IRB, peer reviewed, and first to note associated mutations in genes affecting the ECS and neurotransmitter systems that may elucidate the pathophysiology of these adverse events [8]. **Keywords:** DNA, genomics, genotyping, personalization, endocannabinoid, terpenes, cannabinoids.

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P-6

Hexahydrocannabinol: review of the chemistry and pharmacology of an understudied cannabinoid

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Introduction: Hexahydrocannabinol (HHC; 6a,7,8,9,10,10a-hexahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b*,*d*]pyran-1-ol) of unspecified stereochemistry was first prepared in the respective laboratories of Adams and Todd in 1940. HHC and delta-9-THC (THC) bear close structural similarity but the pharmacology of HHC has scarcely been studied. HHC, which is not scheduled by international drug treaties, has emerged in the drug market as a constituent of infused hemp flower, edibles and vape products in the USA and elsewhere from around mid-2021. **Aims:** This presentation provides a concise review of the chemistry and pharmacology of HHC. **Methods:** A systematic review of scientific literature was done by conducting an exact structural search in SciFinder for HHC, as well as textual searches for «hexahydrocannabinol» and «HHC» in PubMed and GoogleScholar. (Cautionary note: «HHC» has also been used as an acronym of 9-nor-9-hydroxyhexahydrocannabinol.) **Results:** HHC is a non-natural and relatively stable cannabinoid. It can be prepared by total synthesis, by hydrogenation of delta-8/delta-9-THC isolated from cannabis, or by hydrogenation of the acid-catalysed cyclization product of cannabidiol obtained from low-THC industrial hemp. HHC may also co-occur with cannabinol (CBN) in aged cannabis-samples. Cannabis-derived HHC is typically a mixture of 9-alpha- and 9-beta-methyl stereoisomers (epimers) which have different pharmacological properties. Limited preclinical studies, conducted since 1940 and recently supported by anecdotal users' reports, indicate that HHC produces THC-like effects. Specifically, behavioural experiments with rhesus monkeys indicate that it is the 9-beta-methyl epimer, or (6a*R*,9*R*,10a*R*)-HHC, which is mainly responsible for the cannabinoid-like effects being about half as active as delta-9-THC. The metabolism of HHC has been studied only in animals and data on its toxicology or safety are lacking. **Conclusions:** The human pharmacology of HHC is virtually unknown. Consequently, further preclinical research as well as clinical studies are needed to explore the full biological activity spectrum and the therapeutic potential of HHC. **Keywords:** Cannabis sativa, hemp, hexahydrocannabinol, pharmacology, stereochemistry.

P-7

Dissecting the roles of cannabidiol and cannabidiolic acid in triple negative breast cancer cells

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Introduction: Breast cancer is the most frequently diagnosed cancer in women worldwide. Currently 3 subtypes of this disease have been identified estrogen receptor (ER)-positive, which is positive for the biomarker ER alpha. HER2, which is positive for Human Epidermal Growth Factor Two (HER2) and generally negative for ER and the progesterone receptor (PR) and triple-negative breast cancer (TNBC), which is negative for ER, HER2 and PR. Triple negative tumors are deficient for well-defined molecular targets making chemotherapy, which is non-specific and

cytotoxic, the most common treatment option. Patients with TNBC tend to develop metastasis and recurrence after treatment as well as lower survival compared to patients with other subtypes of breast cancer. Hence, there is a need for innovative therapeutic interventions to help women with breast tumors. Cannabinoids are products of *Cannabis sativa* L. They were first introduced as palliative medicinal products, aiding in reducing emesis resulting from chemotherapy for cancer patients. Cannabinoids possesses anti-tumoral activity in breast cancer cell lines. **Aims:** In this study we tested the effects of CBD and CBDA, natural fitocomplexes extracted from *Cannabis sativa*, on the growth of triple negative breast cancer cells, MDA-MB-231. **Methods:** *In vitro* assays were performed on triple-negative MDA-MB-231 cells treated with cannabidiol (CBD) (1, 5, 10, 20, 40 and 80 μg/mL) and cannabidiolic acid (CBDA) (1, 10, 20, 40, 80, 160 μmol/L), alone and in combination. The effects of CBD and CBDA on viability were determined by wound healing and MTT assays, while cell migration was assessed by transwell migration. **Results:** Cell proliferation, viability and apoptosis of MDA-MB-231 cells were impaired by CBD and CBDA. Specifically, our data show that CBD and CBDA reduced the proliferation of MDA-MB-231 cells by impairing cell-cycle progression ($p<0.05$). These findings suggest that the combination of these cannabinoids may represent a new strategy for the treatment of patients suffering from triple-negative breast cancer. **Conclusions:** These findings suggest that the combination of CBD and CBDA may represent a new strategy for the treatment of patients suffering from TNBC and TNBC related pain. **Keywords:** Cannabinoids, cannabidiol, cannabidiol acid, breast cancer, proliferation. **Acknowledgements:** We thank Dr. Alessandra Trocino and Mrs. Mariacristina Romano from the IRCCS G. Pascale of Naples, for giving bibliographic service and support. We thank Dr. Ana Serrato Head Drug Development of Avextra Group AG for financial support to attend the congress.

P-8

Assessing the metabolic diversity of cannabis chemovars cultivated in Colombia

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Introduction: The cannabis plant is a natural biosynthetic factory of «pharmacological cocktails» that exert distinct and valuable therapeutic effects on a composition dependent matter [1]. Cannabis metabolites have been proposed to simultaneously modulate diverse biological systems, including the endocannabinoid system (ECS). Access to standardized, metabolically diverse, and reproducible cannabis chemotypes (known as chemovars) is essential for physicians to optimize individualized patient treatment. However, decades of selective breeding have reduced the germplasm and metabolic output of cannabis available for patients, narrowing its therapeutic potential. New sources of genetic and metabolic diversity are needed. **Aims:** Towards contributing to the diversification of medicinal cannabis, we aim to identify chemically distinct chemovars that may have developed unique traits as an adaptative response to the diverse ecological niches throughout the Colombian tropical-Andean region. We aim to gain valuable insights into the chemotaxonomic classification of Colombian cannabis and the influence of cultivation region on the metabolic output of the plant. **Methods:** 131 cannabis flower samples from diverse ecological niches in Colombia were donated by licensed cultivators and analyzed using state of the art liquid and gas chromatography. We performed a targeted metabolomics statistical analysis on a selected subset of 10 cannabinoids and 23 terpenoids. **Results:** Our preliminary data suggest four different chemotypes present among the medicinal cannabis cultivated in Colombia. 31% of the samples were classified as THC-dominant (Type I), 12% as THC:CBD balanced (Type II), 48% as CBD-dominant (Type III), and 9% as CBG-dominant (Type IV). Type III samples showed a solid correlation ($r_{Spearman} = 0.81$) between total THC and CBD levels, but never exceeded 1% w/w of THC. The most abundant terpenes in our samples were α-pinene, limonene, myrcene, β-pinene, terpinolene, linalool, neridol, α-bisabolol, β-caryophyllene and α-humulene. Exploratory cluster analysis showed positive correlations between α- and β-pinene ($r_{Spearman} = 0.91$) and β-caryophyllene and humulene ($r_{Spearman} = 0.97$) which was consistent with previous studies [2,3]. **Conclusions and Outlook:** Most cannabis chemotypes provided by legal cultivators to our study so far are predominantly Type III with total THC levels below 1% w/w. These samples meet the legal definition of non-psychoactive cannabis in Colombia (total THC <1.0%). However, less than 50% of these samples meet the legal definition of non-psychoactive in Europe (total THC <0.2%). Next, we are aiming to evaluate the effect of the diverse cultivation regions throughout Colombia on the metabolic output of the plant and to contributing to building the scientific framework for future cannabis applications. **Keywords:** Cannabinoids, terpenes, metabolomics analysis, chemovars, Colombian cannabis. **Acknowledgments:** We thank Universidad Icesi for project funding through the grant COL0093872-1061 «Diversidad metabólica del cannabis en Colombia». The authors express their gratitude to Dr. med. Alexandros Livadas for sponsoring the IACM conference participation of D.J. Enriquez.

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P-9

Development of novel photopharmacological tools for investigating the involvement of *h*CB_1R in disorders associated with the endocannabinoid system

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Introduction: The human cannabinoid receptor type 1 (*h*CB_1R) plays important roles in the regulation of the perception of pain, locomotor and appetite control, development of addictive behaviours as well gastrointestinal and reproductive functions. Activation of *h*CB_1R with high spatiotemporal control is useful to study processes involved in different pathologies related to nociception, metabolic alterations, and neurological disorders. A possible strategy to generate tunable probes to selectively modulate *h*CB_1R in a time and tissue specific manner is photopharmacology. Here, the activation of a ligand can be modulated by the application of light irradiation to generate a reversible rearrangement in its molecular structure, which changes its pharmacological activity [1]. **Aims:** We aim to develop novel photopharmacological probes targeting *h*CB_1R that act as «molecular switches» to allow optical control in receptor activation/ deactivation studies with high spatiotemporal control. **Methods:** By applying azo-derivatization strategies, a series of *h*CB_1R modulators were designed and synthetized based on the backbone of SR1411716A (rimonabant) and an indole core to yield photoswitchable *h*CB_1R antagonists and agonists, respectively. The novel compounds were evaluated by radioligand binding studies, calcium mobilization, receptor internalization, cell luminescence assays, sensor receptor activation (GRABeCB2.0), western blots analysis for ERK1/2 activation, NanoBiT βarr2 recruitment and molecular docking. **Results:** We obtained a *h*CB_1R antagonist **1** (photo-rimonabant, Fig.1a) which shows marked affinity for the receptor ($K_{i\ (cis\ from)}$ = 29 nM) [2], whose potency increases by irradiation with ultraviolet light (*h*CB_1R K_i *trans*/*cis* ratio = 15.3). Additionally, we developed the «*cis*-on» photo-agonist **2** (Fig.1b) which shows high affinity for *h*CB_1R ($K_{i\ (cis\ from)}$ = 0.18 μM) [3], with a marked difference in affinity with respect to its less active «*trans*-off» form (*h*CB_1R K_i *trans*/*cis* ratio = 5.4). **Conclusions and Outlook:** Our research allowed us to understand the molecular characteristics necessary to design photoswitchable *h*CB_1R agonist and antagonists with optimal pharmacological properties. Respectively, compounds **1** and **2** are a new class of photoswitchable agonist and antagonist for *h*CB_1R that serve as molecular tools for investigating the involvement of the receptor in disorders associated with the endocannabinoid system with high spatiotemporal control. **Keywords:** Photopharmacology, cannabinoid receptor, G-protein-coupled receptor, CB1 modulators, optical control **Acknowledgments:** We thank the German Research Foundation (Deutsche Forschungsgemeinschaft) under DFG DE1546/10-1 for project funding and the German Academic Exchange Service (Deutscher Akademischer Austauschdienst, DAAD) for a Ph.D. scholarship for D.A.R.-S and for a «Research stays for university academics and scientists» scholarship for Y.A.R.

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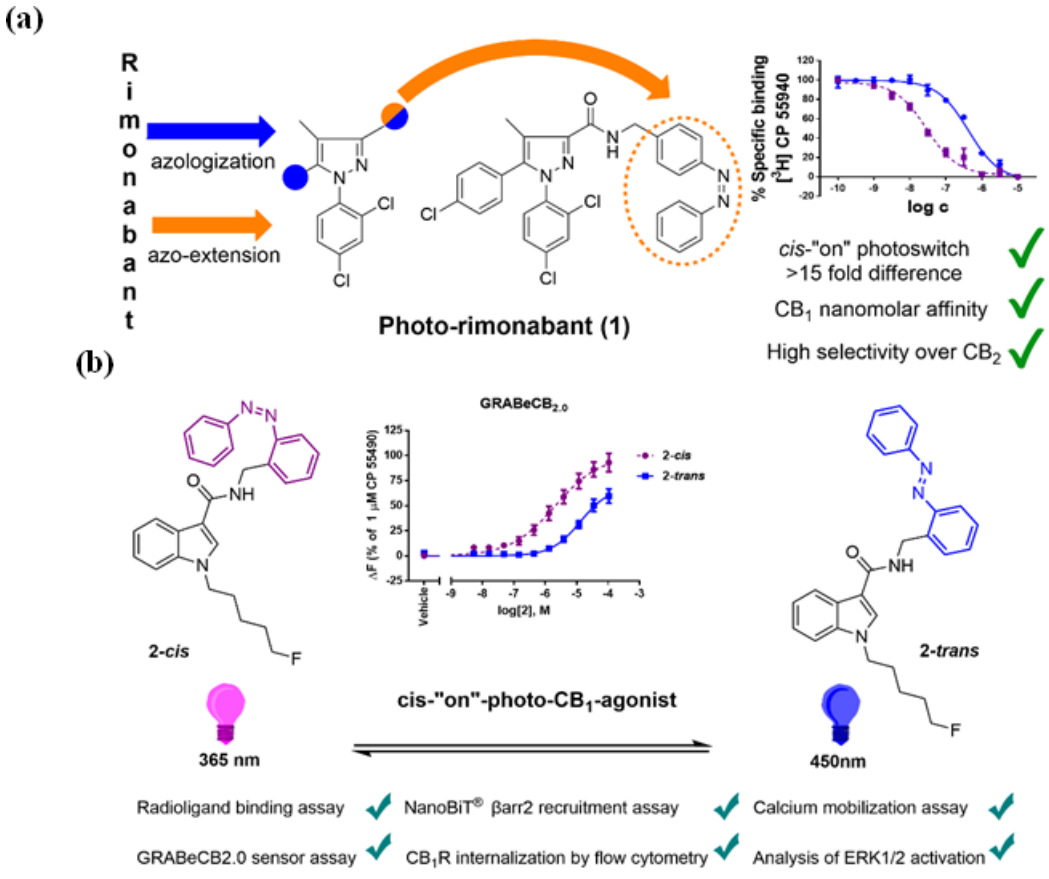

Fig. 1. (a) *h*CB_1R Photo-switchable antagonist «photo-rimonabant» (**1**). **(b)** «*cis*-on» photo-*h*CB_1R-agonist (**2**).

P-10

Long-term follow-up of THC/CBD oil treatment for severely demented patients: acceptability and safety

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Introduction: The interest in cannabinoids in Alzheimer's disease and other forms of dementia has increased. Some clinical studies confirm that cannabinoids might be of interest for managing the behavioral and psychological symptoms of dementia (BPSD). Still, to our knowledge, there is a lack of studies conducted with a natural oil formulation containing a combination of tetrahydrocannabinol (THC) and cannabidiol (CBD) at a fixed ratio. Also, the long-term safety of medical cannabis administration in vulnerable populations and real-life data about the clinical improvements are lacking. **Aims:** The first objective of this study was to investigate the feasibility and the long-term safety of administering a cannabis medication containing a standardized quantity of THC and CBD to patients with severe dementia and living in a nursing home. The secondary objective was to collect information on clinical outcomes. **Methods and Results:** This is a prospective observational study (auth n 2017-001196 Geneva CCER) of 19 patients with severe dementia and BPSD living in a long-term home facility in Geneva. They received a THC : CBD 1 : 2 oil for 13 months at increasing dosages, starting from an average of 7.2 mg THC : 14.4 mg CBD per day. The average dosage was 12.4 mg THC : 24.8 mg CBD daily after 13 months. Side effects were rare and mild, and none of the patients stopped the treatment for side-related effects of CBD or THC. Clinical evaluations were conducted every 2 months on scores assessing patients' behavioral troubles and rigidity, and they all showed a marked improvement, which was stable during the whole observation period (Fig. 1). Moreover, at least 1 drug deprescription was made possible for 84% of patients. **Conclusions:** Our study shows that natural cannabis oil, standardized in THC and CBD content (THC : CBD ratio 1 : 2), can be safely administered to patients with dementia for over a year without serious adverse reactions. The observed clinical

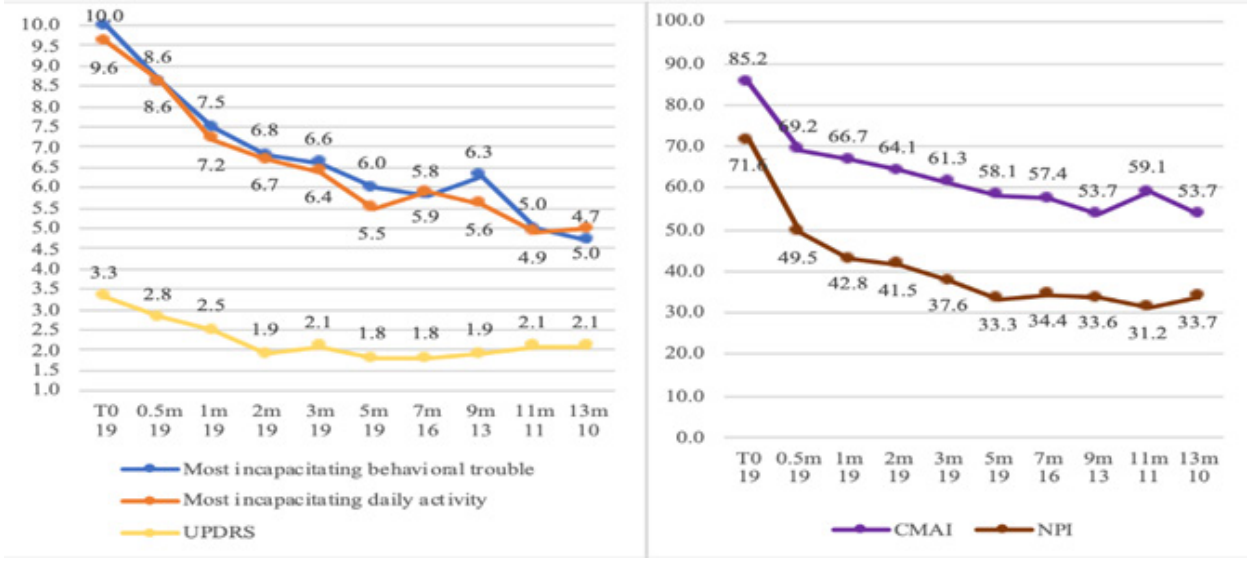

Fig. 1. Clinical evaluation of patients' troubles and rigidity.

improvements and deprescription need to be confirmed in a prospective randomized controlled clinical trial, planned based on this study's data (NCT05432206). **Keywords:** Cannabinoids, medical cannabis, THC/CBD oil, dementia, long-term care. **Acknowledgements:** We warmly thank all the health professionals, nurses, and staff in "residence Les Tilleuls" for their assistance and advice throughout the study, especially Ms. Angeline Langlois, nurse clinician.

P-11

Pharmacokinetic evaluation of cannabinoids co-prescription in elderly with polyprescription

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Introduction: Cannabinoids' pharmacokinetic interactions with the CYP450 enzymes might affect other drugs' metabolism, as shown in *in vitro* and *in vivo* studies. Still, humans pharmacokinetic data are scarce. Moreover, older adults are more exposed to polypharmacy (>5 treatments a day) and have an increased risk of drug-drug interactions. **Aims:** The objective of this study was to conduct an observational pharmacokinetic evaluation to assess the potential for drug-drug interactions in a population of polymedicated aged patients with dementia taking a THC/CBD medication for more than a year. **Methods and Results:** 15 patients with severe dementia receiving a THC/CBD treatment were assessed for the potential pharmacokinetic drug interactions with the Geneva cocktail approach [1]. The enzymatic activity of the cytochromes P450 (CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4/5) was measured at 2 time-points about 6 months apart. The enzymatic activity of the CYP1A2 and CYP2C19 showed a slowdown with a phenotyping switch between the two blood samplings, where no concomitant drugs could explain the results observed (Metabolic ratio mean±SD: CYP1A2 1st sampling = 0.26 ± 0.11, 2nd sampling = 0.20 ± 0.09; CYP2C19 1st sampling = 0.55 ± 0.38, 2nd sampling = 0.44 ± 0.44SD). CYP3A4 enzymatic activity remained stable between the two blood samplings, and no other phenotyping switches were observed (Metabolic ratio mean ± SD: CYP3A4 1st sampling = 0.89 ± 0.32, 2nd sampling = 0.85 ± 0.27). Therapeutic drug monitoring of THC/CBD was measured at a steady state in 18 patients, characterizing the plasma through levels of THC (mean ± SD = 1.3 ± 0.7), its 2 metabolites 11-OH-THC (mean ± SD = 1.9 ± 1.7), and free THC-COOH (mean ± SD = 55 ± 28.1), and CBD (mean ± SD = 2.5 ± 1.3). The mean plasma THC-COOH concentrations showed that the treatment was regularly taken and well absorbed, still, no accumulation of THC, metabolites, or CBD occurred over time. **Conclusions:** Patients tolerated well the cannabinoid intake with a favorable safety profile. A slight reduction in some hepatic enzymatic activity was observed, but no severe adverse events related to the treatment or concomitant drugs were reported. Moreover, no drug discontinuation was observed due to side effects. Inhibition of the CYP3A4 activity is suggested in the SmPC for nabiximols at high dosages or over time. However, the CYP3A4 enzymatic activity was almost unchanged in our cohort, even despite a long period of medication intake. **Keywords:** Cannabinoids, medical cannabis, THC/CBD oil,

pharmacokinetics, drug-drug interactions **Acknowledgements:** We thank Zacharie Patà, Aline Mina, and Fettouma Kerrouche for helping collect the data. Also, we would like to thank the families for their support.

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P-12

TRPV2 correlates with endometrial cancer aggressiveness and its activation by cannabidiol induces cytotoxicity and improves chemosensitivity

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Introduction: Endometrial cancer (EC) is the most diagnosed gynaecological malignancy in developed countries and comprises type I endometrioid EC and type II non-endometrioid EC, the most aggressive and with poor prognosis [1]. Treatment options have limited efficacy, mainly in relapsed or metastasized EC. Transient Receptor Potential Vanilloid 2 (TRPV2) has been associated with altered tumour cell proliferation, invasiveness, and aggressiveness, in fact is often dysregulated in tumours [2]. Cannabidiol (CBD), is considered a TRPV2 agonist, and was studied for its anti-tumoral effects in many human cancer models [3]. **Aims:** TRPV2 expression in EC biopsies and EC cell lines and the effect of CBD-induced TRPV2 activation in EC cell line models. **Methods:** Evaluation of TRPV2 expression in EC cell lines by RT-PCR and western blot and in EC biopsies by immunohistochemistry. Analysis of TRPV2 correlation with Overall Survival (OS) and Progression-Free Survival (PFS) by Kaplan–Meier analysis. TRPV2 transfection and CBD-induced activation to evaluate the effects on cytotoxicity, migration, and chemosensitivity, by cell viability, wound healing, gene and protein expression profiles analysis. **Results:** Results show that EC malignancy correlates with high expression of TRPV2, that is associated with shorter PFS. TRPV2 transfection increased migration, Akt phosphorylation and improved response to cisplatin. CBD induced cell death, mainly by apoptosis in type I cells and autophagic-cell death in mixed type EC cells. CBD improved chemosensitivity, with higher efficacy in TRPV2 over-expressing EC cell lines. **Conclusions:** Data evidence that TRPV2 expression increases EC aggressiveness, suggesting its potential use as diagnostic marker in EC. Moreover, seen the effect of CBD on EC cell lines, these data suggested its potential use, in a promising strategy, as adjuvant therapeutical drug. **Keywords:** Cannabidiol, endometrial cancer, TRPV2, chemoresistance. **Acknowledgements:** Fondazione Umberto Veronesi (Post-doctoral Fellowship 2021-2022), UNICAM School of Advanced Studies in Life and Health Sciences.

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P-13

Anticancer effects of cannabidiol and oxygen-ozone combination in human pancreatic ductal adenocarcinoma cell lines

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Introduction: Pancreatic Ductal Adenocarcinoma (PDAC) is an aggressive and lethal malignancy. Surgical resection followed by adjuvant chemotherapy is the main therapeutic strategy, but it is less effective in high-grade patients, so new therapies are necessary [1]. The use of cannabidiol (CBD), was evaluated in *in vitro* and *in vivo* models in several human cancers [2]. Oxygen-ozone (O_2/O_3) therapy is an emerging alternative tool use to ameliorate mechanisms promoting chronic pain and inflammation. **Aim:** To evaluate the anticancer effects of CBD and O_2/O_3, alone and in combination with chemotherapeutic drugs, in 2 human PDAC cell lines. Expression profile of CBD-target receptors (CBD-TRs) and their correlation with Overall Survival (OS) and Recurrence Free Survival (RFS) in PDAC patients. **Methods:** Cytotoxicity was evaluated by MTT assay. Cell death mechanism by cytofluorimetric and western blot analysis. PDAC gene profile modulation was evaluated with TaqMan Array. CBD-TRs gene and protein expression levels were evaluated by RT-PCR and western blot analysis. By Pan-cancer database, OS and RFS associated to CBD-TRs expression in PDAC patients were determined. **Results:** CBD and O_2/O_3 induced cell death in PANC-1 and MIAPaCa-2. Moreover, CBD and O_2/O_3 increased chemotherapeutic drugs efficacy. CBD and O_2/O_3 modulate the expression profile of PDAC involved genes. The expression profile of CBD-TRs in PDAC cell lines was determined: PANC-1 showed a higher expression of TRPV2 receptor, while in MIAPaCa-2 TRPV4 was the higher CBD-TRs expressed. Finally, database results showed a significant correlation between OS and RFS, and specific CBD-TRs expression levels. **Conclusions:** These preliminary data suggest that CBD and O_2/O_3 combined therapy could be used as adjuvant to chemotherapy and specific CBD-TRs should be potential targets as diagnostic markers and in PDAC therapy. **Keywords:** Pancreatic cancer, cannabidiol, TRPV channels, chemotherapy, oxygen-ozone. **Acknowledgements:** Fondazione Umberto Veronesi (Post-doctoral Fellowship 2021-2022), UNICAM School of Advanced Studies in Life and Health Sciences, "Maria Guarino" Foundation—AMOR No Profit Association.

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P-14

Cannabinoids ameliorate inflammation and reduce keratinocytes hyperproliferation in a psoriatic skin model

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Introduction: Cannabidiol (CBD) and cannabigerol (CBG) are two of the main pharmacologically active phytocannabinoids of *Cannabis sativa* L., exerting a variety of beneficial pharmacological effects. Their anti-inflammatory activity has been studied using different experimental models of inflammation, exhibiting the capacity to decrease the production of pro-inflammatory cytokines and chemokines and to reduce inflammatory cell infiltration [1]. Psoriasis is an example of an inflammatory skin condition where cannabinoids could have a positive impact due to its interaction with cannabinoid-1 (CB_1) and cannabinoid-2 (CB_2) receptors, and overall anti-inflammatory properties. **Aims:** The overall objective of this research proposal was to explore the potential of CBD and CBG as bioactive ingredients for skin health improvement in an inflammatory psoriatic skin model. **Methods:** After evaluating cannabinoids' impact on different psoriatic primary cells, an inflammatory psoriatic-like skin model containing both dermis and epidermis was optimized using skin explants and a cocktail of inflammatory cytokines. A healthy skin explant was used as control. Immunohistochemistry analysis of inflammation and keratinocyte hyperproliferation mediators - hallmarks of psoriasis, was performed to validate and evaluate both psoriatic and healthy models. Different concentrations of CBD and CBG on a squalane and sunflower oil formulation were evaluated for their therapeutic potential. Gene expression profiles were also assessed. **Results:** The psoriatic-like skin model was successfully stablished, as confirmed by the expression of different psoriatic markers. More importantly, both cannabinoids led to a reduction on the production of several pro-inflammatory cytokines, namely IL-6, IL-1α, IL-17 and TNF-α, as well as on different markers of keratinocyte hyperproliferation (e.g., keratin 6, 16 and 17, PI 3-kinase, and psoriasin). Moreover, neither CBD nor CBG led to significant alterations in the extracellular matrix of the healthy skin model. **Conclusion:** Considering the results attained using the psoriatic-like skin model, as well as in the *in vitro* assays, the use of CBD and CBG as promoters of skin health seems to be a logical and promising choice when searching for novel therapeutic candidates. These compounds were able to ameliorate inflammation and keratinocytes hyperproliferation, while not damaging the skin structure, demonstrating its safety. However, further research is still needed to solidify these findings. **Keywords:** Cannabidiol, cannabigerol, psoriasis, anti-inflammatory, *ex vivo* model. **Acknowledgments:** This research was funded by National Funds from FCT Fundação para a Ciência e a Tecnologia through project UID/Multi/50016/2019 and from ANI Agência de Inovação through project Alchemy (POCI-01-0247-FEDER-027578).

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P-15

Systematic review of clinical pharmacokinetics of THC following consumption of different cannabis products

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Introduction: Delta-9-tetrahydrocannabinol (THC)-containing cannabis products are used for medicinal purposes by wide populations of patients. THC has been reported to have variable pharmacokinetics following consumption by different routes, which limits its clinical safety and effectiveness, and requires extensive titration and monitoring of patients that use cannabis products. There are substantial differences in the exposure to the THC and in the values of its pharmacokinetic parameters that were reported in different clinical trials. **Aims:** To retrieve and assess the available clinical data on the pharmacokinetics of THC in human subjects or patients following consumption of different cannabis products. **Methods:** Publications on clinical pharmacokinetics of THC were retrieved from the PubMed database, C_{max} and AUC of THC and its metabolites, and subjects' demographic data were retrieved according to the PRISMA guidelines. These data were summarized and analyzed to reveal the extent of the available data and its variability. **Results:** We identified 39 publications that matched the search criteria and included quantitative data on C_{max} and AUC of THC and its metabolites. Majority of the retrieved datasets were small (mean: 18.84, 95% CI [12.43, 25.25]), originated from young volunteers (25 datasets, mean: 29.55, 95% CI [26.73, 32.37]), mostly male, cannabis-naïve or with previous experience with cannabis. The investigated products were cigarette, inhaler/ vaporizer, and oral/oromucosal (31, 17, and 10 datasets, respectively). C_{max} and AUC of THC and of its metabolites were highly variable, within the individual datasets, and between the datasets. **Conclusions:** THC is characterized by high inter-subject pharmacokinetic variability, following consumption of

different cannabis products. The extent of intra-subject variability cannot be assessed based on the available data, and requires further investigation. THC pharmacokinetic data in patients are scarce, and no conclusions regarding the THC pharmacokinetic variability in relation to patients' age, gender, genotype/phenotype, disease state, etc. can be made based on the available data. More rich pharmacokinetic THC data from clinical trials in patients with different diseases, and "real world" data are needed to reveal the extent of the inter- and intra-subject pharmacokinetic variability of THC and to identify the variability factors. **Keywords:** THC, cannabis, pharmacokinetics, variability factors, systematic review.

P-16

Medical abbreviations and acronyms related to cannabis and cannabinoids

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Introduction: Accurate recognition of medical abbreviations and acronyms is essential for patient safety. Studies have shown that abbreviations and acronyms may lead to medically-dangerous misinterpretation. In fact, as part of hospital accreditation the Joint Commission surveyors are screening health records to assure medication names appear in long-from. Open access repositories of medical terms have been instrumental in reducing the use of abbreviations that may lead to clinical errors. **Aims:** To show the breadth of risk that may be associated with two cannabinoid specific abbreviated medical terms. **Methods:** We chose the common terms 'CBD' and 'THC' to show possible medication names and other abbreviations sharing the same acronyms. Using the python programming language, we have searched open access databases including Meta-inventory, a database of 104,057 medical abbreviations and DrugBank a database of 14,752 drugs, for the cannabis related terms identified previously. Similarly, we performed cross-mapping of medication names that have interactions with cannabis. **Results:** The two acronyms and related long forms are shown in Table 1. Consequently, we identified in Drugbank 1,784 names of medications that have interactions with cannabis and cannabinoids, out of which 904 had abbreviations. The mean number of long forms for each of those abbreviations is 11.72 with 95% CI [10.72, 12.72]. **Conclusions:** Many medications and a hazardous chemical contain the abbreviations CBD and THC. Adding the long form in parentheses and clearly indicating whether or not the term refers to a cannabinoid, may prevent lay people from accidentally accessing chemicals containing these acronyms in hope for lightheadedness or pain relief. As cannabis related medications and other cannabinoids (as CBG, CBC, CBN) become more main stream, this practice will be enforced down the line and early adaptation may be beneficial. **Keywords:** Cannabinoids, abbreviations, patient safety, medical informatics, quality assurance.

Table 1. Cannabis- and cannabinoids-related terms, abbreviations

Abbreviation	Long forms Medical
CBD	Cyclobutadiene, Calgary Biofilm Device, Cannabidiol, Calcipotriol-Betamethasone Dipropionate, Carbendazim, Cyclobutadiene
THC	Tetrahydrocannabinol, Tetrahydrocortisol, tetrahydrocurcumin, tetrahydrochrysene, tiaramide hydrochloride, Tetrahydrochrysene, (R,R)-5,11-diethyl-5,6,11,12-tetrahydro-2,8-chrysenediol, 4-tetrahydoroxychalcone (chemotherapy), terpin hydrate and codeine, Tetrahydrocortisone, Tetrahydrocoptisine, Thiacloprid , Tiaramide hydrochloride, Trihexosylceramide

P-17

The picture of medical cannabis in Germany painted by patients' words and gender differences

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Introduction: Since March 2017, the number of German patients prescribed cannabis medical products grew. **Aims:** To assess German patients' free text narratives about medical cannabis therapy. **Methods:** We conducted a nationwide, anonymous survey on medically prescribed cannabis products. Patients answered standardized questions online in a text dialog ("chatbot") and had the option to write free text. We used Python to process the text using standard natural language processing (NLP) techniques to remove common words. Consequently, we calculated word frequencies in the full cohort and in two sub-cohorts. **Results:** We distributed brochures with a hyperlink to the online questionnaire through a network of 50 cannabis pharmacies and patient organizations. Of the 1'580 participants who interacted with the questionnaire, 1'035 provided consent to use their answers for research purposes. A sub-cohort of 292 participants (193 male, 99 female) wrote free text of more than 32 characters. **Conclusions:** Almost one-third of the participants used the optional free text field, which suggests important content to express in their own words. Word frequency analysis indicates focus on the clinical outcomes of the treatment and also a concern about its cost and reimbursement from statutory health insurance. In Table 1, 4 terms refer to cost ('kostenübernahme', 'krankenkasse', 'kosten', 'krankenkassen'), with a higher proportion reported by males for all of them. In female narratives there is a higher rate of clinical terms. This initial result requires further advanced NLP analysis. **Keywords:** Cannabis, natural language processing, patients' survey, Germany.

Table 1. Frequent Terms Used by Cannabis Patients and Mean Frequencies by Sex

Term	Male	Female	P-value	Term	Male	Female	P-value
cannabis	0.4	0.43	0.297	kosten	0.08	0.06	0.405
blüten	0.08	0.13	0.149	wirkung	0.05	0.11	0.060
schmerzen	0.08	0.12	0.154	lebensqualität	0.05	0.09	0.119
nebenwirkungen	0.1	0.08	0.358	cannabistherapie	0.02	0.11	0.079
kostenübernahme	0.08	0.08	0.264	krankenkassen	0.06	0.04	0.272
krankenkasse	0.09	0.05	0.152	thc	0.04	0.06	0.498

P-18

Extraction and formulation of bioactive compounds from *Cannabis sativa L.* using deep eutectic solvents

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Introduction: Poor aqueous solubility of the terpenophenolic compounds (phytocannabinoids) cannabidiol (CBD) and cannabidiolic acid (CBDA) is a major issue in the widespread use of these therapeutic molecules. Cannabinoids are highly lipophilic (logP of ~6), resulting in very low solubility in water and susceptibility to extensive first pass metabolism. Consequently, the reported biovailability for these compounds are low, thus presenting a major problem for product design and formulation. The development of aqueous solubility-enhanced formulations may lead to higher CBD bioavailability [1]. Deep eutectic solvents (DESs) comprising or acting as solvents of active pharmaceutical ingredients (API-DESs) have been used to design polymeric drug delivery systems, enhance dissolution rates, increase membrane permeability, and improve transdermal delivery [2]. **Aim:** The aim of this work was to design new DESs that could work simultaneously as green extraction solvents and as delivery systems for cannabinoids. **Method:** Cannabinoids from hemp flowers and leaves were extracted using hydrophilic and hydrophobic DESs based on amino acids, terpenes and fatty acids. The solubility of the produced extracts was evaluated in PBS at 37°C for 24 h to simulate the physiologic conditions. **Results:** Initial screening showed that the hydrophobic DES had a greater extraction efficiency of CBD + CBDA of all the tested DESs. Menthol:lactic acid (2:1 M ratio) presented higher extraction yields than ethanol. However, these systems did not improve the solubilization of cannabinoids in PBS. Hydrophilic DESs presented a higher CBD + CBDA solubility in PBS when compared to cannabis oil and hydrophobic DESs. Lactic acid:glucose (5:1 M ratio) and proline: lactic acid (2:1 M ratio) presented the highest solubility of all tested DESs. These systems are capable of dissolving in PBS, acting as a carrier for cannabinoids and increasing its solubility. **Conclusion:** Besides having a higher or equivalent extraction yield as ethanol, DESs showed to be more selective, extracting fewer impurities and capable of improving cannabinoids solubility. These results demonstrated that the use DESs in extraction and final formulation represent a better alternative to organic solvents and an advantage for future therapeutical applications. **Keywords:** Cannabis sativa, green extraction, deep eutectic solvents, cannabinoids, plant extracts.

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P-19

Cannabidiol as a potential treatment for migraine: preliminary data in an animal model

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Introduction: Clinical and preclinical data have suggested a deregulation of the endocannabinoid system in migraine pain. Furthermore, modulation of this system may reduce trigeminal excitability. Cannabidiol (CBD), a phytocannabinoid devoid of psychoactive effects found in *Cannabis sativa*, has recently gained much attention due to its antioxidant, antiinflammatory and analgesic properties. **Aims:** 1) To evaluate accumulation of CBD in cranial areas that are involved in migraine pain in rats treated chronically; 2) to test whether a single CBD administration reduces hyperalgesia in an animal model specific for migraine. **Methods:** Four sets of male Sprague-Dawley rats (n=5 for each

experimental group) received CBD 15 mg or 30 mg/kg for 5 consecutive days. Rats were sacrificed 1 h or 24 h after the last administration and the meninges, medulla, cervical spinal cord and trigeminal ganglia were quickly dissected out to evaluate CBD levels by online-SPE LC-MS/MS. In another set of rats (6-7 per group), we tested the effect of a single dose of CBD (15 mg/kg, i.p.) in the nitroglycerin (NTG)-based animal model of migraine. Rats were treated with CBD or its vehicle, 3 h after NTG or vehicle injection and were exposed to the orofacial formalin test 1 h later. **Results:** We found the elevated levels of CBD in all areas under evaluation after chronic treatment. As expected, the levels were higher 1 h after the last treatments, than after 24 h, thus suggesting that CBD does not accumulate in these tissues. Interestingly, the single acute administration of CBD significantly reduced NTG-induced trigeminal hyperalgesia. **Conclusion:** These data offer key information on the distribution of CBD in the meninges and in central and peripheral nervous system areas involved in migraine pain. They also suggest the capability of the compound to modulate migraine-related nociceptive transmission. **Keywords:** Cannabidiol, trigeminal hyperalgesia, migraine. **Acknowledgements:** Cannabidiol was provided by Curaleaf International.

P-20

Effects of cannabidiol on migration and reactive oxygen species production in bacterial lipopolysaccharide-primed human polymorphonuclear leukocytes

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Introduction: Cannabidiol (CBD), the main non-psychoactive cannabinoid of *Cannabis sativa*, is widely used in the treatment of inflammation and pain related to different type of local and systemic disorders. Polymorphonuclear leukocytes (PMN) are the first immune cell to be recruited into inflammatory sites, and CBD extensively affects their functions [1-3]. PMN may undergo a process called "priming" [4], consisting of two different steps: (i) cell exposition to priming agents, therefore being recruited into inflamed tissues; (ii) where they encounter activating stimuli and become fully activated. Priming, described in different immune-mediated diseases, is associated with a wide range of changes including production of pro-inflammatory mediators, such as reactive oxygen species, PGE2, and cytokines [4]. **Aim:** In this study, we investigated the ability of CBD on PMN migration and reactive oxygen species (ROS) in bacterial lipopolysaccharide (LPS)-primed cells. **Methods:** Experiments were performed in human PMN isolated from buffy coats of healthy donors with CBD used at non cytotoxic concentrations as previously described [1] and cells were cultured under resting or primed/stimulated conditions (LPS and fMLP). LPS was used as priming agent and PMN migration and ROS production were measured. **Results:** In resting PMN, CBD (0,1-10 μM) did not affect migration and ROS production. Priming was induced by treating cells for 1 h with LPS (1000 ng/mL), which per se was unable to affect ROS generation or cell migration. LPS priming increased fMLP (0,1 μM)-induced ROS production ($P<0.01$ vs fMLP alone, $n = 7$) and cell migration ($P<0.01$ vs fMLP alone, $n = 5$). CBD (1 μM) prevented the effects of LPS priming on both ROS production ($P<0.05$ vs LPS + fMLP; $n = 5$) and cell migration ($P<0.05$ vs LPS + fMLP, $n = 5$). **Conclusion:** CBD extensively affects human PMN functions at non-cytotoxic concentrations: 1 μM indeed represent the concentrations achieved with doses used in clinics to treat certain forms of epilepsy [5]. The present study extends our previous observations showing the anti-inflammatory activity of CBD on some PMN functions [1-3]. Results indicate that CBD counteracts the effects of priming on key functions such as migration and ROS production, strengthening its therapeutic potential in inflammatory disease. **Keywords:** Cannabidiol, human PMN, inflammation, pain. **Acknowledgements:** This study was supported by Curaleaf International, UK.

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P-21

The effect of a novel phytocannabinoid on estrogen receptor activity in breast cancer models

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Introduction: Breast cancer is the most frequently diagnosed type of cancer and the leading cause of cancer-related death in women worldwide. It is not a single disease, but rather multiple subtypes with different biological features and distinct pathological and clinical implications. Tumors that express estrogen receptor alpha (ERα) and depend on estrogen for cell proliferation constitute 60%-70% of all breast cancer cases. Patients with ER-positive tumors are advised to receive systemic endocrine therapy to block ER activity. Common endocrine therapy for this kind of breast cancer is Selective Estrogen Receptor Modulators

(SERMs) such as tamoxifen. However, such therapies are associated with adverse effects that bring about patient non-adherence to treatment. Concurrently, cannabis consumption for medical use is increasing worldwide. One of the major indications for which patients have been prescribed cannabis is the relief of chemotherapy-associated side effects. However, the clinical effects of cannabinoids are not clear and it seems that their potential is greater than initially thought, raising the interest in their clinical application. **Aims:** Harness the utility of cannabinoids in treating ER-positive breast cancer. **Methods and Results:** A large screen of different cannabis extracts ensued a specific cannabis chemovar, CANN14, that sensitizes ER-positive breast cancer cells to the cytotoxic effect of the SERMs. Of that extract, a novel phytocannabinoid was identified that can mimic the effect of the whole extract without any toxicity by itself. This novel phytocannabinoid, termed 373.15b, affected estrogen signaling by decreasing the protein and mRNA expression levels of ERα and reducing its transcriptional activity. Combined treatment of 373.15b and low doses of tamoxifen reduced tumor volumes and weights in an *in vivo* model in which slow-release estradiol pellets were implemented subcutaneously to the dorsal flank of female nude mice. Phytocannabinoid 373.15b was effective in sensitizing breast cancer cells only to SERM-type inhibitors, including also toremifene citrate and 4-hydroxytamoxifen, demonstrating the specificity of the phytocannabinoid to ER expression and signaling. **Conclusion:** Phyocannabinoid 373.15b is a promising co-therapy candidate for decreasing the treatment dosage of conventional therapy, thereby diminishing its associated side effects and improving patient quality of life. **Keywords:** Breast cancer, phytocannabinoid 373.15b, tamoxifen, *in vivo*.

P-22

Long COVID, the mysterious disease: A role for cannabidiol

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Introduction: Long COVID is a mysterious condition characterised by a plethora of symptoms lasting 3 months but usually longer after the onset of the acute infection. Although its cause and mechanisms are still incompletely understood, current hypotheses favour an immunopathological nature leading to a multi-inflammatory, multi-organ syndrome that can persist for months or even for years. **Aims:** The potential role of cannabidiol (CBD) is briefly reviewed. **Methods:** Publications on potential targets of CBD were reviewed. **Results:** A number of *in vitro* and *in silico* studies suggest that CBD may be able to target processes that are crucial for the infection of host cells by SARS-CoV-2. Given as an example, CBD seems to inhibit SARS-Cov-2 spike (S) protein-induced cytotoxicity and spike protein expression (even 2 h after infection) [1]. In addition, CBD seems to inhibit other steps important for the infection process that have still not been completely clarified, such as proteases that facilitate the infection process. Moreover, CBD reduces inflammation also in patients with SARS-CoV-2 infections [2] and has demonstrated benefits in a wide range of symptoms commonly observed with long-COVID (e.g., anxiety, sleep disorders, post-traumatic stress, diffuse pain, chronic fatigue, cognitive impairment). As long COVID seems to be fuelled by persisting and/or newly formed antigens that trigger inflammatory responses at the side of tissue attacks by antigens, the immunomodulating properties of CBD that have been demonstrated in several models of Autoimmune Disorders are of particular interest (examples: Multiple Sclerosis, T Cell-Mediated Chronic Autoimmune Myocarditis, Diabetes Mellitus Type 1 or Rheumatoid Arthritis) [3]. **Conclusions:** CBD is a multitarget substance with interesting pharmacological properties. It easily crosses also the intact blood-brain barrier, has anti-inflammatory properties and demonstrated immunomodulating effects in various immunopathological conditions. Although human experiences in Long COVID are still missing, CBD seems to be a promising substance. **Keywords:** Cannabidiol, Long COVID, SARS-CoV-2, autoimmune disorder, inflammatory disorder.

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P-23

Proposing cannabis-based medication in severely demented patients: unexpected symbolic and relational effects for the family caregivers

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Introduction: There is a lack of therapeutic options for patients with severe dementia, but cannabis-based medication (CBM) has potential benefits. For the introduction of CBM in this patient group, consent is needed from family caregivers or legal representatives. In the context of a clinical pilot project on the use of THC/CBD oil, we added a sociological component to investigate the expectations and observations of family caregivers. **Methods:** Semi-structured interviews (n=31) by a trained sociologist with family caregivers (n=22), before and after the introduction of a CBM to severely demented patients with behavioral disorders, in a specialized care setting in Geneva, Switzerland. **Results:** All family caregivers consented to the CBM for their relatives and were unexpectedly positive about the proposal, suggesting a high level of confidence in the care setting. They seemed to see it as a social reconsideration of their excluded and "lost" parent/partner: "at

least we're trying something". Expectations on the anticipated effect of CBM on the patient's physical and behavioral problems were high, and sometimes disappointed. Still, the perceived effects also allowed reinvestigating the family-relative relationship, weakened by the illness, and reshaping it. **Conclusions:** In our context, the acceptance by family caregivers of CBM for elderly patients with severe dementia was high. Beyond a possible clinical impact on the patients, the introduction of CBM has unexpected symbolic and relational effects on their family caregivers and should be accompanied. **Keywords:** Dementia, family caregivers, expectations, relationships, cannabis-based medications. **Acknowledgements:** We thank the families for their support.

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SwissCanOn – patient registry for medicinal cannabis in oncology

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Introduction: Worldwide, cannabis-based medicinal products (CBMP) are becoming an increasingly popular alternative to established supportive medicinal products in cancer related symptoms including chemotherapy-induced nausea and vomiting, pain, anxiety, insomnia, anorexia, in acute and palliative care. Although there is preclinical data supporting the hypothesis of cannabinoid analgesia and further positive influence in several indications, clinical evidence is limited leading to several uncertainties. **Aims:** The registry SwissCanOn is a multicenter, binational, prospective, patient registry that aims to collect comprehensive real-world data in Switzerland (CH) and Germany on prescription, usage and effectiveness of CBMP in the treatment of refractory oncological indications, including patient reported outcomes. **Methods:** The first data assessment period is scheduled for two years and plans to include at least 100 patients. At patient's registry inclusion, physicians collect data such as diagnosis, medical treatment, etc. in a web based and mobile health application, patients download the corresponding patient App and continuously enter their information on dosage, symptoms (ePROs), wellbeing, cognition, vital signs, etc. A CME certified medical education on CBMP is offered for participating medical doctors throughout the project and cooperation between all stakeholders is strongly supported. **Results:** A first and purely descriptive data presentation with 6 patients in CH shows that 50% of patients stopped registry participation early due to either side effects or preference for non-medicinal cannabis. **Conclusions:** This first data presentation shows that the SwissCanOn registry is an adequate method to (1) collect a sustainable data basis for a variety of different research questions, (2) serve as a solid basis leading to further clinical investigations, (3) create a growing network of patients, academic and industrial partners emphasizing science, (4) allow physicians to track efficacy and side effects of CBMP therapy with their patients, and (5) associate the project with an academic program on medicinal cannabis. **Keywords:** Medicinal cannabis, oncology, scientific patient registry, real-world data. **Acknowledgements:** Project supported by Swiss Alpinopharma GmbH, Mobile Health AG, MedCan.ch.

P-25

Phytocannabinoids for the treatment of Parkinson's and Huntington's Disease - Neurodegenerative conditions presenting hyperkinesia

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Introduction: We performed a literature review focused on the potential of whole plant-based cannabinoid formulations in the treatment of Parkinson's Disease (PD) and Huntington's Disease (HD); two conditions that present debilitating dyskinesias against a background of neurodegeneration. Two lines of enquiry are explored in this review: (1) the potential of tetrahydrocannabinol (THC) to reduce hyperkinesia and (2) the potential of phytocannabinoids to ameliorate neuroinflammation and other neuroprotective mechanisms. **Aims:** The aim was to explore whether phytocannabinoids could have the potential to address a predominant symptom (hyperkinesia) and ameliorate the underlying component of the pathology (neurodegeneration). **Methods:** A comprehensive review of Embase and Medline databases was performed, and all available clinical evidence was assessed for selected cannabinoid therapies in each condition. Pre-clinical evidence was selected to explore the pathophysiology of the condition in relation to the endocannabinoid system and mechanisms of action of promising phytocannabinoids. **Results:** Our review of changes in the endocannabinoid receptors (CB_1 and CB_2) over the course of the disease informs our assessment of the clinical data and our recommendations for future clinical trial design. Trials in HD were likely confounded by short treatment duration, inappropriate patient populations and dose ranges. Trials in PD were likely confounded by patients with complex dyskinetic symptoms and a poor selection for patients where hyperkinesia predominated. Previous trials and reviews were made difficult to interpret by presenting a mix of cannabinoids, agonists and antagonists, in the same context; it is possible to disentangle the data set and analyse effects more precisely. By assessing the potential neurogenerative and protective properties of a variety of cannabinoids, we see a rationale to favour full-spectrum extracts over synthetic isolates. **Conclusions:** There is sustained interest in academia and patient groups for the use of cannabinoids in the treatment of PD and HD. Lessons can be learnt from previous trials and pre-clinical data to fine-tune future clinical trials for subsets of HD and PD patients. The use of plant-based, full-spectrum formulations is potentially supported by multiple, complementary neuroprotective actions of phytocannabinoids which would benefit from further research. **Keywords:** Cannabinoids, Huntington's Disease, Parkinson's Disease, neuroinflammation, hyperkinesia.

P-26

Sex difference in cannabinoid therapy – Literature review

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Introduction: As the use of medical cannabis continues to increase, prescribers and other healthcare professionals need to know as much as possible about characteristics that may affect treatment, such as age, co-occurring use of other drugs and sex. **Aims:** To provide the necessary basis for further research on sex differences in the treatment with medical cannabis. **Methods:** Literature review of publications addressing how sex affects metabolism and effects of medical cannabis. **Results:** The analysis of the preliminary data from the first large German non-interventional survey of medical cannabis users suggests a difference in gender response to medical cannabis [1]. A more in-depth literature search indicates, among others, differences in the density of the cannabinoid receptor CB1 in several areas in male and female brains. The availability of CB1 increases in women with age [2]. Moreover, animal studies suggest a reduction in NMDA receptors in females after adolescent THC exposure. Males respond with a higher expression of NMDA receptors [3]. In addition, men and women exhibit different metabolism of 11-OH-THC, the primary metabolite of THC [2]. **Conclusions:** Our literature review indicates that there are gender differences in response to medical cannabis therapy. These could be due to different metabolism and receptor expression in both sexes. Future analysis of data from clinical studies and non-interventional surveys should examine phenotypic differentiation between the sexes in cannabis efficacy for different symptoms, side-effects and pharmacokinetics, in order to enable patient- and gender-specific therapies with medicinal cannabis. **Keywords:** Cannabinoids, literature review, precision medicine, sex factors.

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P-27

Metabolomic approach of plasma samples from schizophrenia patients and cannabis consumers

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Introduction: Cannabis abuse is considered a risk factor for the early development of schizophrenia. Although it is generally associated to the endocannabinoid system, a metabolomic approach with a larger scope can be interesting in terms on finding new biomarkers. **Methods:** Metabolites present in plasma of patients of both genres aged between18 and 68 years, with cannabis use disorder, schizophrenia, or a dual diagnosis of schizophrenia and cannabis use disorder, together with the corresponding control groups, were analyzed by liquid chromatography–high-resolution mass spectrometry by means of a non-target approach after a cold extraction using methyl tert-butyl ether. We first extracted and annotated as many compounds as possible using the implemented mass list (HMDB, Lipid Maps) and spectral libraries (mzCloud) in Compound Discoverer (v 3.3). These results, together with the targeted analysis of 8 endocannabinoids (129 metabolites, 104 samples in total) were processed in MetaboAnalyst to study the correlation patterns between the metabolites and the sample metadata (subjects, genre, age) and to identify possible biomarkers. **Results:** The ANOVA2 and linear analysis of the whole dataset showed that most of the analytes (101) were significant towards the groups, but none of them seem to be significant regarding the genre or age. From this observation, we can highlight the presence of two endocannabinoids (PEA, OEA), nicotine and cotinine as biomarkers of tobacco consumption and nor-9-carboxy-Δ9-THC as biomarker of the consumption of cannabis. At a lower significance, we have also found aripiprazole and the metabolite dehydroaripiprazole, one of the antipsychotic drugs that was used in the treatment of the schizophrenic patients. The analysis between each group and the corresponding control samples showed a clearer clustering of the samples. In this sense, for instance, some medium chain acylcarnitines (C8/C10) share a common pattern in the three comparisons and some *N*-acyl serines were also highlighted in some of the group comparisons. **Conclusions:** In comparison to the classical approach, where only some specific known markers are monitored, the use of metabolomic approach and the workflow used in this work to uncover the biomarkers, provided us a deep insight to evaluate the three groups studied. **Keywords:** Schizophrenia patients, plasma, LC-MS, metabolomics, biomarkers.

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PLGA nanocapsules of cannabinoids: characterization, loading capacity and gastro-intestinal bioavailability

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Introduction: Nanoencapsulation of cannabinoids via poly (lactic-co-glycolic acid) (PGLA) seems a promising option to improve their bioavailability when administered orally while provides a controlled release. **Methods:** 36 different formulations of PLGA-cannabis capsules were synthetized using 3 cannabis phenotypes (CBD rich, THC rich and CBD/THC leveled), 3 cannabis extract/PLGA ratios (10 mg, 30 mg and 60 mg of cannabis extract per 100 mg of PLGA) and 4 coatings (no coating, pectin coating, alginate coating and chitosan coating). In order to assess the suitability of nanocapsules they were fully characterized (particle size, z-potential and scanning electron microscope (SEM) image), the cannabinoid load was measured (concentration of 14 cannabinoids) and gastrointestinal digestion was in-vitro simulated. **Results:** Adequate nanocapsules were synthetized based on the measured parameters regardless of phenotypes and loading quantities: (i) Particle size was between 100 - 200 nm in all cases except from pectin-coated capsules (300 – 400 nm); (ii) Z-potential values were around −20 mV for no coated, −40 mV for pectin and alginate coated and +20 mV for chitosan coated capsules; (iii) all capsules had a spherical or semi-spherical morphology according to SEM images. Mean cannabinoid content of capsules are shown in Table 1. The concentrations refers to the mean of the 4 coatings in each case, as there were no significant differences among coatings, and the coefficient of variation was below 5 % in all cases. *In vitro* simulations showed similar release profiles of cannabinoids in all capsules: between 5 – 15 % of the total content of capsules was released in the gastric phase whereas 10 – 50 % of the total content was slowly released in the first 2 h of the intestinal phase and then steady-state was reached. In overall, CBD/THC leveled capsules showed lower bioavailability comparing to CBD or THC rich capsules; at the same time, bioavailability increased with the decrease of the employed mass of cannabis extract. **Conclusions:** Although all capsules may be suitable for a therapeutic use, those with lower cannabis/PLGA ratio and chitosan coating may be the best choice, as they showed the best bioavailability values and their positive Z-potential could enhance adhesion to the intestinal mucosa. **Keywords:** Cannabinoids, PLGA nanocapsules, intestinal bioavailability.

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What do patients think about cannabinoid-based medicines in palliative care: A qualitative investigation of expectations and barriers

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Introduction: Although there is evidence for the use of cannabinoid-based medications (CBM) in palliative care, only a minority of patients benefit from a prescription. **Aims:** The objective of this study was to explore the perceptions, expectations, and

Table 1. Composition in mass percentage of main cannabinoids in capsules. "Others sum" include the sum of THCA, THCV, CBN, CBNA, CBCA and CBGA content. THCVA, CBDV and CBDVA were not detected

Phenotype	Extract mg per 100 mg of PLGA	CBD % (m/m)	THC % (m/m)	CBG % (m/m)	CBC % (m/m)	CBDA % (m/m)	Others sum % (m/m)
THC rich	**10**	0.1	8.3	0.2	0.2	< 0.1	0.2
	30	0.2	20.3	0.4	0.4	< 0.1	0.5
	60	0.2	35.1	0.7	0.7	< 0.1	0.9
CBD rich	**10**	6.8	0.5	0.1	0.4	0.2	< 0.1
	30	17.0	1.2	0.3	0.9	0.6	< 0.1
	60	26.3	1.8	0.5	1.4	0.9	< 0.1
Leveled in THC and CBD	**10**	4.0	3.8	0.2	0.3	0.2	0.4
	30	8.5	8.2	0.4	0.6	0.5	0.7
	60	14.7	14.3	0.7	1.0	0.9	1.3

experiences of CBM usage among a small group of palliative care patients and to identify different obstacles to prescription. **Methods:** This is a qualitative study using semi-structured in-depth interviews, by a trained physician, in an inpatient palliative care unit in Geneva, Switzerland. The Interpretative Phenomenological Analysis method was used for the analysis. **Results:** Ten patients in palliative care, average 73.3 years (range 55 to 92 years), mainly with advanced cancer, participated in the face-to-face interviews. Most patients were in favor of CBM use in palliative care, and they distinguished it from non-medical use. Seven themes were identified from patients' perceptions, experiences, and expectations during the interviews: right time to begin CBM (use as last option); fears linked to off-label use; lack of information about side effects and of a safe medical framework; high costs and lack of reimbursement; relatives and social acceptance of an "illegal" drug. **Conclusions:** The obstacles described by the patients seem to be surmountable with specific measures at the clinical level. We suggest training health professionals in a palliative care setting, especially in explaining the effects and side effects, and developing clinical guidelines and improved patient information. CBM will undoubtedly play a more significant role in palliative care medicine in the coming years, but reimbursement seems essential. **Keywords:** Cannabis, perceptions, expectations, palliative care, cannabinoid-based medications. **Acknowledgements:** We thank F. Bianchi for her contribution.

P-30

Cannabis and cannabinoids in therapeutics. Part 1: Effects on asthma and inflammation of the respiratory tract

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Introduction: A review of the scientific and medical literature was undertaken to evaluate the therapeutic interest of cannabis and cannabinoids for the treatment of Asthma and Inflammation of the respiratory tract. **Aims:** To establish an understanding of modes of action with the endocannabinoid system; to review the first studies carried out on human subjects in the 1970's and animal models using specific cannabinoids. **Results:** The very first publications on the effects of marijuana smoke demonstrate bronchodilation rather than bronchoconstriction opposite to tobacco smoke as well as opiates and do not provoke respiratory depression [1]. Experimental animal models have demonstrated a reduction of pro-inflammatory cytokines interleukin IL-6 and tumor-necrosis factor TNF; the level of serum Immunoglobulin E (IgE) and overproduction of mucus in the lungs. Cannabidiol (CBD) improves pulmonary function and reduces inflammation of air pathways in mice with acute lung injury [2]. Human studies on oral and inhaled cannabis convincingly show a bronchodilating effect in asthmatic patients. CBD and its synthetic analogues appear as the most promising therapeutic agents due to their mechanism of action and absence of side effects [3]. **Conclusions:** This review shows that cannabinoids and in particular CBD are of benefit for the treatment of asthma and Inflammation of the respiratory tract. Of particular mention is the cannabis-based medicine Asmasol approved by the Jamaican Ministry of Health in 1985 and its generic SATIMOL™ recently developed in Jamaica by Cloud 9 Switzerland and the Caribbean Institute of Pharmacy Policy Practice and Research. **Keywords:** Cannabinoid, asthma, cannabis, cannabidiol.

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P-31

Cannabis and cannabinoids in therapeutics. Part 2: Effects on ocular function

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Introduction: A review of the scientific and medical literature was undertaken to evaluate the therapeutic interest of cannabis and cannabinoids, in particular THC and CBD in the treatment of intra-ocular pressure and glaucoma. **Aims:** To explore the effects of cannabinoids on ocular function, the prevention of glaucoma and protection of the optic nerve. To review the first studies carried out on human subjects in the 1970's and animal models using specific cannabinoids. To review pharmacological formulations with and without THC for topical application. **Results:** The endocannabinoid system appears to play a major role at all levels of the visual system, notably in the regulation of ocular pressure through complex mechanisms involving at least the 3 cannabinoid receptors CB1, GPR18 and GPR19 [1].The first studies showed marijuana smoke rapidly reduced intra-ocular pressure in normal human subjects as well as subjects afflicted with glaucoma. Several animal studies using THC and CBD showed various results both positive and negative depending on mode of application and the animal used. Formulations of THC as microemulsions, nanomolecules and pro-drugs have shown positive results in terms of transcornean penetration and duration of the hypotensive effect while helping to reduce the side effects of THC on the central nervous and cardiovascular systems. Another group of researchers developed formulations without THC capable of reducing intra-ocular pressure, protecting the optic nerve and were successfully used on glaucoma patients [3]. **Conclusions:** This review shows that opthalmic cannabinoid formulations are of benefit for glaucoma patients reducing intra-ocular pressure, protecting the optic nerve and can avoid eye surgery. Of particular mention is the cannabis-based medicine Canasol approved by the Jamaican Ministry of Health in 1983 and its generic SATISOL™ recently developed in

Jamaica by Cloud 9 Switzerland and the Caribbean Institute of Pharmacy Policy Practice and Research. **Keywords:** Glaucoma, THC, CBD, Cannabis sativa.

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P-32

Untargeted metabolomics approach to predict adaptability of Cannabis sativa L. cultivars to tropical stress

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Introduction: Innovative biotechnological approaches have turned to be necessary for setting out plant breeding projects, taking into consideration the unpredictability of plant performance due to the changing climate and external factors. In these circumstances, metabolomics may shed light in plant adaptability studies, as biomarkers relating plant performance with the surrounding environments could be identified in plant metabolisms. Nevertheless, little literature around untargeted analytical methods and protocols could be found when keeping record on metabolomic screening of cannabis. **Aims:** Therefore, a HPLC-HRMS based untargeted analytical method was optimized. Two different objectives can be found in this work: i), to develop a proper procedural protocol for untargeted metabolomics screening of cannabis which offers the broadest metabolomic coverage without leaving aside unequivocal identification of compounds; ii), as proof of concept, to run a series of field cultivations in both control and tropical stress conditions (high temperature and humidity) and to perform metabolomic research on them in order to find potential biomarkers of cultivars' adaptability to tropical conditions. **Methods:** A bottleneck type decision-making workflow was followed, in which extractants, chromatographic column and biological tissue under study were optimized, respectively. Five different extractants, 3 chromatographic columns and 3 plant tissues (leaf, flower and stem) were studied. Once the analytical method was optimized, a field cultivation of 2 cannabis varieties was run, in which 36 clones of each variety were grown in both control and tropical stress conditions, and samples were collected periodically every 2 weeks for untargeted metabolomic analysis. **Results and Conclusions:** The broadest metabolomic coverage was observed via $CHCl_3$:MeOH:H_2O (50:25:25 v/v) extraction, using a C18 chromatographic column for analysis, and disposing of the information obtained from stems. This method was applied in the metabolomics field-experiment. After applying differential analysis between groups ($p \leq 0{,}05$), a PLS-DA classification model was built with the significant metabolites, to observe the VIPs. Preliminary results on leaf tissue showed that metabolite ratios diethylhydroxylamine/N-acetyl-D-glucosaminate and 11-amino-undecanoic acid/1-18:3-2-18:3-digalactosylacylglycerol could have potential as biomarkers of cultivar adaptability to tropical growth environment (Figure 1). Once the complete result data is acquired, more field cultivations will be run, implying more cultivars, keeping record of potential biomarkers already identified. **Keywords:** PLS-DA (Partial Least Squares Discriminant Analysis), VIP (Variable Importance in Projection), ROC curves (Receiver Operating Characteristic curves).

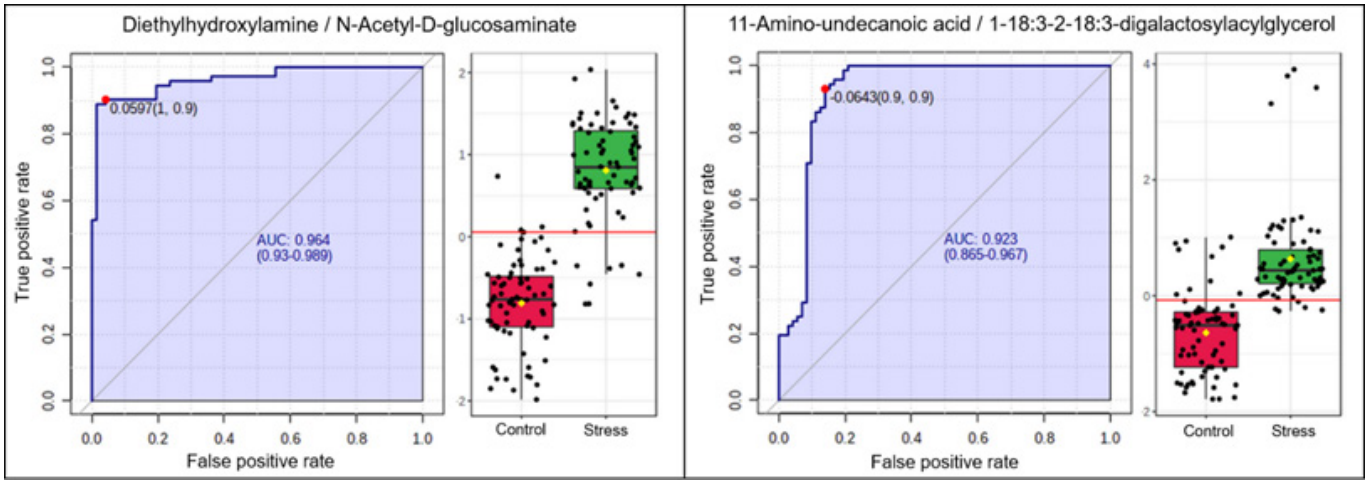

Fig. 1. Metabolite relantionships' ROC curves, showing significant differences between control and stress growth environments.

P-33

Hyperspectral imaging and machine learning for non-destructive chemotype classification in *Cannabis Sativa L.*

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Introduction: In cannabis industry, cannabis cultivars are usually characterized by their cannabinoid profile and generally classified depending on the concentration or ratios of the major cannabinoids present in their metabolism: Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD), alongside their acidic conjugates (THCA and CBDA, respectively). According to both cannabinoid ratios, 3 major chemotypes could be distinguished in cannabis: chemotype I, which possesses high THC and low CBD contents; chemotype II, with balanced concentrations of both cannabinoids; and chemotype III, whose THC and CBD concentrations are low and high, respectively. If consumed, these chemotypes can induce diverse effects. Therefore, a general procedure could be summed up for cannabis characterization: flower harvesting, sample drying, solid-liquid cannabinoid extraction and subsequent analysis by LC-DAD, or alternatively, by NIR. This means that the analytical procedure is destructive. **Aims:** The objective of this work was to develop a preliminary in-field characterization procedure, which should be simple and did not imply sample destruction, thus, analysis could be made directly *in vivo*. Consequently, hyperspectral imaging was used for cannabis chemotype characterization. **Methods:** Hyperspectral images were taken with a HySpex SWIR-384 camera, using the 3-m lens configuration. Images of 6 cannabis cultivars, 10 individuals from each, were taken at sunlight, from which 3 were cultivars of chemotype I, 2 were chemotype II, and 1 was of chemotype III. Images were read with Hyper-Tools 3.0 graphical user interface and data analysis was performed with PLS_Toolbox 9.8. A PLS-DA classification model was built with the collected data. **Results:** The model showed ROC curves of the 3 different chemotypes, in which a clear chemotype differentiation can be observed. Specificity and sensitivity values are 0.9515 and 0.9215 for chemotype I group, 0.9796 and 0.9725 for chemotype II and 0.9849 and 0.9548 for chemotype III (Figure 1). **Conclusion:** A clear differentiation between chemotypes was observed using hyperspectral imaging, which clears the future for the development of *in field/in vivo*, non-invasive, analytical tools. **Keywords:** LC-DAD (Liquid Chromatography-Diode Array Detector), PLS-DA (Partial Least Squares Discriminant Analysis), NIR (Near-Infrared Spectroscopy), ROC curve (Receiver Operating Characteristic curve).

P-34

The neuroprotective potential of Henola, Białobrzeskie and Tygra Cannabis sativa varieties

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Introduction: Cannabis sativa L. is a plant of various varieties that may exhibit significant potential for biological activity with antioxidant, anti-inflammatory, analgesic, anxiolytic, antitumor activity, anticonvulsant, antiemetic, immunomodulatory, and neuroprotective activity [1]. **Aims:** The aim of the research was to determine the variety of the raw material from various varieties such as: Henola, Białobrzeskie, Tygra. The leaves and inflorescences of the cultivars were analyzed. The extracts used in the study of antioxidant activity were obtained as a result of extraction in the supercritical phase with carbon dioxide. **Methods:** Dry raw

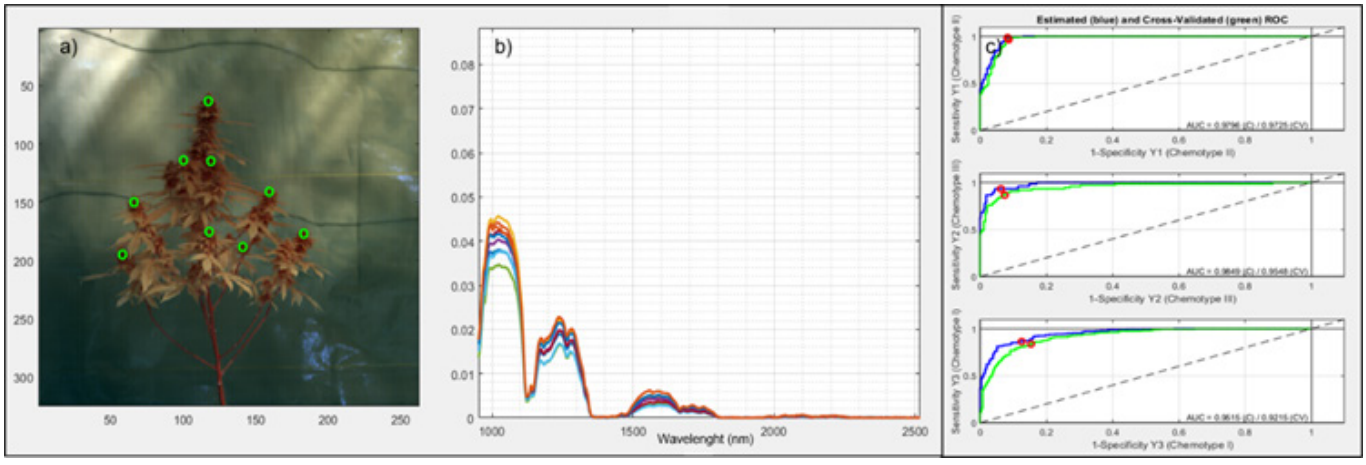

Fig. 1. a) Hyperspectral image of a chemotype II cultivar. **b)** Spectra retrieved from the marked pixels in the **(a)** image. **c)** Obtained ROC curves of the 3 chemotypes.

material was ground and placed in an extraction vessel. The dynamic supercritical CO_2 extraction process was performed under 2000 and 6000 psi at 50°C. Next , the extracts were suspended in methanol, winterized, and filtered. Cannabinoids' (CBD, CBDA, CBG, CBGA, Δ^9-THC, THCA, CBC, CBN) contents were measured by HPLC-DAD. The antioxidant potential was determined by using DPPH, ABTS, CUPRAC, and FRAP procedures. The potential to inhibit the enzymes influencing the development of neurodegenerative diseases, such as acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), was also studied. **Results and Conclusions:** Extracts obtained under 6000 psi showed higher cannabinoid content and more substantial neuroprotective potential than extracts obtained under 2000 psi. The greatest summary content of all 8 cannabinoids were found in Tygra inflorescence extract obtained under 6000 psi. As expected, the most significant antioxidant potential was provided by the same extract. However, AChE and BChE were the most efficiently inhibited by Henola inflorescence extract obtained under 6000 psi (in which the highest cannabinoid content was CBD – 6.027 mg/g dry raw material). **Keywords:** Cannabis, supercritical fluid extraction, antioxidant activity, neuroprotection. **Acknowledgments:** This research was funded in whole by National Science Centre, Poland, the grant Preludium nr UMO-2021/41/N/NZ7/01125.

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P-35

The impact of mixed versus individual strain composition on the long-term stability of cannabinoids in medicinal cannabis-based oils

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Introduction: Cannabis is a monospecific genus that includes two subspecies and a multitude of varieties, resulting from naturally-occurring and artificially-produced strains. As part of their sourcing strategies in supply chain models, manufacturers of balanced delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) medicinal cannabis-based oils may opt for genetically distinct Cannabis strains to formulate the finished, standardised products, often in the absence of stability studies for each possible permutation of strain constituents. **Aims:** To test whether medicinal cannabis-based oil products having a mixed strain composition significantly impact the long-term stability of cannabinoids when compared to their individual constituent strain products. **Methods:** Stability data was extracted from a total of 5 studies submitted for regulatory review; 3 on products with an individual strain composition and 2 on mixed strain products. Cannabinoid assay results were generated under long-term conditions in compliance with ICH Q1A(R2) criteria, having intervals for testing and product pack size as constant variables. The raw data was operated in 4 discrete comparative studies where the THC or CBD concentrations of the mixed strain products were analysed against each individual constituent strain product. The datasets were tested for normal distribution and inferential statistical tests for the cannabinoid content were performed at a confidence level of 95%. **Results:** Three of the 4 datasets were found to be normally distributed, where the Independent Samples T-Test was used to check for significant differences between the stability data, with the remaining study resorting to the non-parametric Mann-Whitney U Test. All 4 comparative studies resulted in a statistical p-value greater than 0.05 (0.328, 0.355, 0.398 and 0.166), indicating that the difference between the cannabinoid content of the mixed and individual strain products throughout the long-term stability period is not statistically significant. **Conclusions:** Since the long-term stability of the cannabinoid profile was not impacted by the strain mix, the inference is that individual constituent strain assay stability studies can act as surrogate for those products of mixed strain composition. **Keywords:** Cannabis, oils, strain, long-term sability.

P-36

Development of lipid composite systems for CBD delivery: solid microspheres by CO_2 cryospraying technology

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Introduction: Cannabidiol (CBD) oral bioavailability is low (<10%), limited by poor solubility, high lipophilicity, instability to gastric pH and first-pass effect. These limitations can be addressed by novel microparticulate systems designed to (i) rapidly disperse in aqueous media, (ii) limit CBD exposure to gastric pH, (iii) maintain CBD in a soluble, microemulsified form in the small intestine, to improve absorption via intestinal lymphatics. CBD microspheres were prepared applying CryoXpand® technology, based on rapid expansion of liquid CO_2 as freezing, atomizing and drying agent to produce micronized powders from sprayed fluids. **Methods:** Preformulation aimed to (i) achieve high CBD solubility in excipients combinations in molten state (40°-60°C), (ii) predict processability by simulating CO_2 exposure (fast-freezing), (iii) study self-emulsification of CBD-excipients combinations at 37°C to select best composites. Selected combinations were processed by CryoXpand®, applying specific pressure, temperature and flowrate parameters. Microparticles were characterized by thermal analysis, their size and morphology studied by SEM. CBD loading, molecular integrity and release were analyzed by RP-HPLC. CBD release from microspheres was studied in acidic and neutral media. Behavior of microparticles in aqueous media was observed by optical microscopy. **Results:** Promising formulations with high CBD loading (>30%) were produced. Microparticles showed good flowability and excellent dispersibility in water (>50 mg/10 mL of water, 30 s). SEM showed spherical microparticles (<100 μm), with matrix-like structure and compact surface. Observed microspheres surface modification upon exposure to water suggested specific mechanisms of CBD release from lipid-composites. CBD dissolution tests in acid medium (pH 1.2) showed minimal release

(1.5%-6.8% at 60 min) indicating drug protection from gastric fluids. Whereas at pH 6.8 microparticles facilitated CBD dissolution: at 15 min, 35% of CBD was released from microspheres vs. 8% of pure drug; at 60 min, release was 52% and 20%; at 120 min 63% and 25% respectively. **Conclusions:** Composite microspheres to improve CBD bioavailability were designed as water-dispersible delivery systems with high drug load. Powders are directly suspensible in drinks or food, or processable into final dosage forms like capsules. CBD dosing can be easily personalized as required by specific therapeutic indications or special patients groups (pediatrics, geriatrics), facilitating patients handling and compliance without complicated formulation or process adjustments. **Keywords:** Microspheres, CBD, bioavailability, lipids, cryo-spraying.

P-37

Accessing the THC and CBD content in oral and inhaled medical marijuana products in Florida's dispensaries

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Introduction: Since legalization of medical marijuana (MMJ) in Florida, the number of certified MMJ users has increased from 26,968 in August 2017 to 741,454 in August 2022. This rise has been paralleled by a vast assortment of available MMJ products, but little is known about their delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) content. **Aims:** To examine types and information on THC and CBD content of oral and inhaled MMJ products available in Florida dispensaries. **Methods:** For each licensed MMJ treatment center in Florida, we randomly selected one dispensary location and visited their website to identify available products. For oral and inhaled products, we extracted product name, price, strain, product form, package size, amount of THC and CBD. Following the most common labelling of products, we listed the THC and CBD content for products forms that are predominantly inhaled in percent, and for edibles as mg THC and CBD per unit. A unit was defined as provided on the website. Finally, for tinctures we standardized the unit to 1 mL. **Results:** We identified 1876 unique MMJ products from 18 dispensaries; among those were 660 extracts, 618 herbals (flowers and pre-rolls), 296 concentrates and 302 edibles (e.g., chews, chocolates). The average percent THC in herbals was 17.8% (range 0.7-33.5%) and 0.3% (range 0.0-16.2%) of CBD (Figure 1). Concentrates had on average 70.6% THC (range 17.6-93.0%) and 1.1% (range 0.0-44.2%) CBD. The highest average THC concentration was found in extracts with 75.1% (range 4.0-97.9%) and 2.4% CBD (range 0.0-74.7%). Edibles had an average of 10.6 mg THC per unit (range 1.0-50.0 mg) and 9.5 mg CBD per unit (range 0.0-10.0 mg). Across all products, 30% lacked quantitative information on CBD content and 4.7% lacked quantitative information on THC content. **Conclusion:** The THC content of examined products in MMJ dispensaries is higher than what has been investigated in clinical trials. THC:CBD ratios are highly skewed toward THC, products with a high CBD content are scarce, information regarding CBD content is often missing. THC content per unit in edibles exceeded the suggested 5 mg standardized unit definition, although the definition of a unit was not always available from dispensary information [1]. **Keywords:** Medical marijuana dispensaries, THC and CBD content, edibles, inhaled MMJ, dose. **Acknowledgement:** This study was supported by the Consortium for Medical Marijuana Clinical Outcomes Research.

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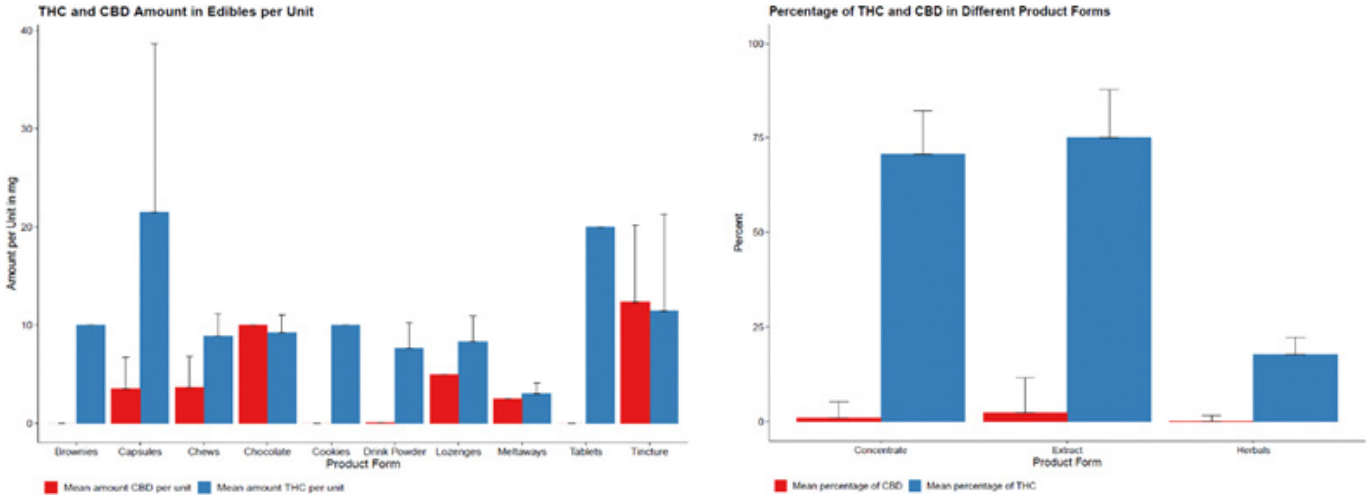

Fig. 1. CBD and THC percentage in different MMJ product forms, and amount in edibles per unit. The upper limit of the standard deviation is shown as error bars.

P-38

Effects of cannabis oil on metabolic disorders in female rats fed a sucrose-rich diet

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Introduction: In recent years, the therapeutic properties of cannabinoids have generated great expectations in society. Cannabis has been used as a herbal remedy for tens of centuries to treat various diseases and symptoms. The main components of Metabolic Syndrome (MS) are dyslipidemia, elevation of arterial blood pressure, dysregulated glucose homeostasis, abdominal obesity and insulin resistance. Several studies have experimentally demonstrated that rats fed sucrose-rich diet display many of the metabolic changes observed in the human MS phenotype. **Aims:** In this study, we evaluated the effects of cannabis oil administration on some metabolic disorders in female rats fed a sucrose-rich diet. **Methods:** Female Wistar rats were fed for 21 days with the following diets: Reference Diet (RD): standard commercial laboratory diet, sucrose-rich diet (SRD) and SRD+Cannabis Oil (SRD+Ca): SRD with the oral administration of 1 mg/kg b.wt. of cannabis daily. Cannabis oil was obtained from mature inflorescences of the CAT1 variety, which contained a 1:2 ratio of THC:CBD. **Results:** The animals of the three experimental groups not presented changes in body weight and energy intake during the experimental period. The incorporation of cannabis oil to the SRD significantly increased ($P<0.05$) analgesia, and also significantly decreased locomotion, which was increased in the SRD group. There were no significant differences in body temperature and catalepsy. Systolic and diastolic blood pressure decreased during the experiment, completely normalizing after 15 days. In the SRD+Ca group, serum levels of triglycerides decreased significantly, reaching values similar to the DR group, without changes in glucose and cholesterol serum levels. Visceral adipose tissue index did not differ between the groups. **Conclusion:** Our results suggest that cannabis oil could be useful as a therapeutic strategy to prevent some of the alterations present in female rats fed a sucrose-rich diet. **Keywords:**Cannabisoil,bloodpressure,catalepsia,dislipemia,sucrose-rich diet.

P-39

A chemical and statistical study of the correlation between cannabinoid and terpene biosynthesis in Cannabis sativa

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Introduction: A synergy effect between cannabinoids and terpenes in cannabis potentially has significant health benefits, as reported in the literature [1]. Patients using medical cannabis tend to choose specific cultivars based on more factors than just cannabinoid content. Terpenes and cannabinoids are produced through the isoprenoid biosynthesis system. Monoterpenes and cannabinoids have a common 10-carbon isoprenoid structure, known as the geranyl diphosphate (GPP), where sesquiterpenes are produced from 15-carbon isopreoid farnesyl diphosphate (FPP) [2]. **Aims and Methods:** Flowers from 100 different cultivars of cannabis from a GMP-certified medical cannabis production were collected for analysis. All flower samples were grinded and homogenized to a particle size of <5 mm before extraction with ethyl acetate. The cannabinoid and terpene profiles of all plants were investigated using HPLC and GC-FID, respectively. Statistical analysis of all data collected from the analytical instruments was performed using Principal Component Analysis (PCA), Partial Least-Square regression (PLS) and Partial Least-Square Discriminant Analysis (PLS-DA). **Results:** There is a significant and cultivar-dependent correlation between the content of specific cannabinoids and terpenes, which could explain the preference of some patients towards specific strains of cannabis. **Conclusion:** A better future via cannabis phytochemistry may be an achievable goal through further research on the synergy effect of this versatile plant that may help fulfilling its promise as a pharmacological treatment for various illnesses. **Keywords:** Cannabinoids, terpenes, biosythesis, synergy effect, chemical analysis.

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P-40

Medical cannabinoids (MC) reduce opioid consumption in elderly and prolong survival of palliative patients

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Introduction: The therapeutic effect and tolerability of Medical Cannabinoids (MC) in elderly and geriatric patients under everyday conditions is still poorly understood; moreover, data are missing about the effect of MC on survival in palliative care. **Aim:** Description of current practice of prescription of MC (dronabinol, nabiximols, cannabinoid extracts) and analysis of the effect of MC on opioid prescribing in pain-patients and survival in palliative patients. **Methods:** Patients of one general practitioner's practice were analyzed. Mann-Whitney-U-analysis of the change of the consumption of opioids (morphine equivalent) in pain patients with MC *vs* without MC, further stratified by age and gender. Kaplan-Meier survival analysis of palliative outpatients with MC *vs* without MC. **Results:** *Opioid reduction:* 178 patients (72 yrs in median; 26-96 yrs) with chronic pain were under MC-therapy for 366 days (median; range 31-2590 d). 115 were female (64.8%). Total, 1'001 MC were prescribed, 557 (55.6%) dronabinol as liquid, 328 (32.7%) as full spectrum extracts and 66 (6.6%) as oro-mucosal nabiximols spray. The daily dronabinol as liquid or extracts were 9.6 mg/d (median), and as spray 13.6 mg. The dosage over the time did not change in patients; women requested lower THC-dosages compared to men (8.1 mg vs. 14.8 mg). Only 5 patients stopped MC because of adverse effects (AE). 115 MC-patients also received opioid analgesics with 65 mg/d morphine-equivalents (median). This opioid-dosage was significantly reduced in course of time by 24 mg/d morphine-equivalents and 50%, respectively, independent on MC dosage, age and gender. When compared to a matched comparison group of patients receiving just opioids without MC (n=156), there was a clinically and statistically significant lower opioid dosage in the MC group. *Survival:* 165 palliative out-patients with a survival time of 7 to 365 days (75 yrs in median; range 44-97 yrs) were under MC therapy. The daily THC dosage was 4.0 mg/d (median; range 0.8-12.0). When compared to a matched comparison group of palliative out-patients without MC (n=767), a prolonged survival of 15 days (median) was detected (Fig. 1). A higher dose (> 7.5 mg/d THC) showed a trend towards longer survival. **Conclusion:** Even at high age, patients with chronic pain profit from long-lasting MC and reduction of comedicated opioids, even at low dosages (<7.5 mg/d THC). AE do not limit the chronic use of MC even in the elderly. Moreover, MC is associated with prolonged survival of patients in palliative care.
Keywords: Dronabinol, geriatrics, opioids, pain, palliative care, survival.

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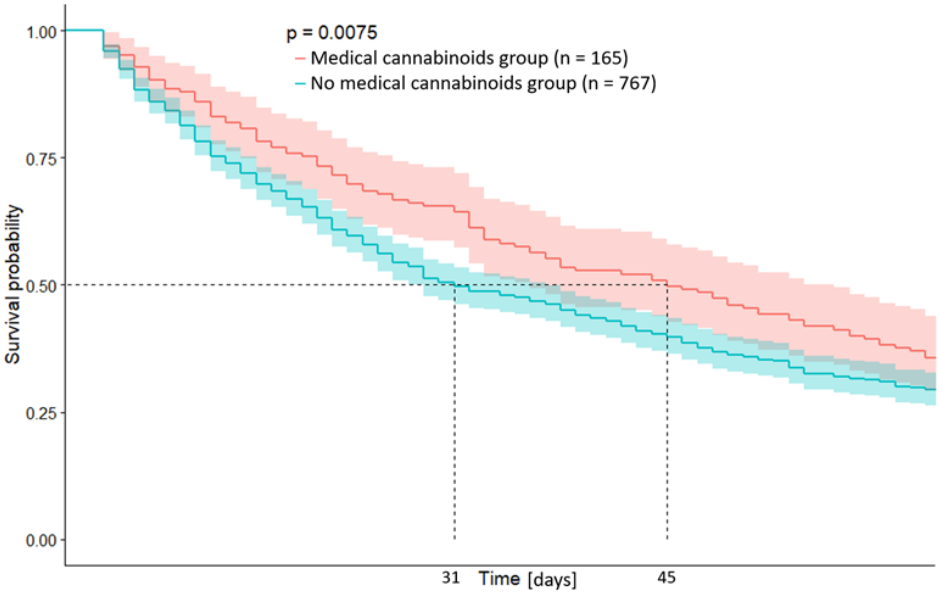

Fig. 1. Survival time of palliative out-patients.

P-41

Cannabidiol as valuable drug in endometrial cancer management

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Introduction: Endometrial cancer (EC) is the seventh most common type of cancer in women worldwide, with most cases occurring between 65 and 75 years of age. Mortality rates have risen by 1.9% per year [1]. According to their histopathological characteristics, ECs have traditionally been divided into two subtypes (type 1 and type 2). An entirely new system based on molecular phenotypes replaces this classification system. According to TCGA, there are four molecular EC subgroups with significant prognostic differences. Considering that the endocannabinoid system has been implicated in the pathogenesis and progression of gynecological cancers, we tested the effects of cannabidiol (CBD) administration in EC cell lines. Additionally, being considered a transient receptor potential vanilloid type 2 (TRPV2) agonist, CBD effects have also been investigated in relation to the expression of such a channel. **Aims:** effects of CBD administration on EC cell lines depending on TRPV2 expression. **Methods:** Kaplan-Meier analysis of progression-free survival (PFS) based onTRPV2 expression using a cohort of 68 EC patients. Evaluation of TRPV2 expression in EC cell lines by western blot. Analyses of CBD administration on cell viability and wound healing to determine its effects on cytotoxicity, migration, and chemosensitivity. **Results:** Results show that EC malignancy correlates with high expression of TRPV2, supporting a possible use of CBD. Indeed, CBD was able to decrease cell viability when administered alone and to increase the anti-cancer effects of cisplatin, doxorubicin and paclitaxel when used in combination. In particular, the higher expression of TRPV2 in PCEM004B with respect to Ishikawa was associated with a higher effect of CBD in inhibiting cell migration. **Conclusions:** Data evidence that the high TRPV2 expression in EC patients with worse prognosis could be exploited administering CBD in combination with standard therapy. **Keywords:** Cannabidiol, TRPV2, endometrial cancer, progression-free survival, migration, chemo-resistance

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P-42

Cannabis sativa L. can reduce inflammation in human keratinocytes thanks to the inhibitory effect of cannabidiol on the NF-κB pathway

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Introduction: Cannabis sativa L. contains high concentrations of cannabinoids including cannabidiol (CBD), the second major cannabinoid and devoid of psychotropic activity, and Δ-9-tetrahydrocannabinol (THC). In our previous study, a Cannabis sativa L. ethanolic extract (CSE), standardized in 5% CBD and low concentration of THC, exerted anti-inflammatory effects in keratinocytes, including the downregulation of genes involved in inflammation [1]. CSE and CBD inhibited the nuclear transcription factor κB (NF-κB), but only CSE showed reduction in interleukin-8 (IL-8) secretion. **Aims:** The aim of the present study was to investigate the contribution of the main constituents of CSE to the biological activities in human keratinocytes, focusing on the NF-κB pathway. **Methods:** CSE and other purified constituents (cannabinoids, terpenes, and cannflavins) were provided by LINNEA SA (Riazzino, Switzerland) and assayed in human keratinocytes (HaCaT) challenged by TNFα. **Results:** CSE was fractionated into 6 sub-fractions and analyzed for the content of cannabinoids, terpenes, and cannflavins. CBD was the most abundant compound, and the inhibitory activity on NF-κB was related to CBD quantity in the fractions. The evaluation of a reconstituted mixture of purified cannabinoids (proportional to CSE), except for THC, inhibited NF-κB comparably to CSE. The mix of terpenes did not show significant inhibition alone or in addition to CBD, not influencing the effect of the single cannabinoid. **Conclusions:** These results suggest that CBD plays a central role in the inhibition of pro-inflammatory mediators in human keratinocytes, acting on the NF-κB pathway. However, other cannabinoids can potentially participate in the anti-inflammatory activity, albeit quantitatively lower than CBD, in particular THC, cannabigerol, and cannabichromene. **Keywords:** Cannabidiol, keratinocytes, inflammation, NF-κB.

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P-43

Tetrahydrocannabinol: Individually customized precision dosage with titration-based adjustments are critical to therapeutic benefits and potential medical value

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Introduction: In this review of available scientific data and documented personal accounts we are reconsidering the concepts of commonly proposed biologically active and subjectively appropriate therapeutic dosages of tetrahydrocannabinol (THC). Unlike most commonly prescribed medications the variability of effective dosage between individuals may be extremely wide. In one observed case for example, one individual found significant beneficial effects from consuming 5 mg of THC, while another individual barely noticed the effects of 200 mg of THC. **Aims:** Here we are carefully investigating various aspects of THC's chemical potency and dosage levels commonly used in clinical studies, medical applications and in personal individual consumption to better understand what may be considered appropriate therapeutically useful doses of THC in order to greatly increase its chances to provide benefits to numerous individuals. **Methods:** By thoroughly reviewing and examining available data and comparing it against commonly reported effects and information shared by medical patients and individuals with both minimal or significant experience consuming cannabis, we have established insightful exciting new ways to think about THC and its applied dosage levels. In light of this information, we offer easy to follow guidelines for attaining precise individually appropriate doses through initiating consumption with very low doses which are increased with titration until desirable results are achieved. **Results:** Our presented information review makes a very strong case for THC having much wider than previously considered potential applications for therapeutic, disease preventive and personal use benefits available to a much larger portion of the current population than the known amount of individuals receiving benefits from it, specifically when effort is used to insure individually appropriate precision dosage is achieved through administering very low doses, which are increased with titration. **Conclusions:** Often seen or referenced adverse reactions to THC are the results of inappropriate dosage levels, rather than inherently negative outcome. THC when administered in very low doses with chronologic titration and subjective feedback allows for significant chances of medical and personal benefits. **Keywords:** Tetrahydrocannabinol, precision, dosage, titration.

Abstracts of Lectures

L-1

Chronic pain as a memory trace - Cannabinoids spark-up therapy

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Acute and chronic pain are different clinical entities. Wheras transient nociceptive stimuli serve a useful biologic purpose (nociception), chronic pain has no biologic purpose, and has to be considered a disease, which outlasts the normal time of healing and has no recognizable end-point. Pain cannot be fully assessed in animal models. However, complimenting the human studies there is now evidence regarding brain reorganization with pain chronification emphasizeing the role of brain plasticity. This reorganization appears pain-type specific in resting state brain activity to acute pain signals but induces more generalized changes with chronic pain syndromes. A transition from a transient to a persistent pain state is a major feature of the ongoing activation and sensitisation of peripheral and spinal nociceptive neurons. Early medication use is protective against development of changes in the central processing circuits which are key to chronic pain as the abnormal persistence of an aversive state. An emotional basis of chronic pain opens a new horizon of opportunities for developing treatment strategies beyond the repeated sole use of acutely acting analgesics. A phase-I trial to determine the pharmacokinetics, psychotropic effects, and safety profile of a novel nanoparticle-based cannabinoid spray for oromucosal delivery highlights a remarkable innovation in galenic technology and urges clinical studies further detailing the huge therapeutic potential of medical cannabis [1]. Given that previously unreported signaling mechanisms for cannabinoids have been uncovered, clinical studies detailing their high therapeutic potential are mandatory. A large body of data has emerged in recent years, pointing to a crucial role of the endocannabinoid system in the regulation of the behavioral domains of acquired fear, anxiety, and stress-coping. Chronic pain may be understood as a disease process evoked by fear-conditioned nociceptive input and appears as the dark side of neuronal plasticity. The anxiolytic and anti-stress effects of medical cannabinoids can substantially modulate the efficacy and tolerability of therapeutic interventions and will help to pave the way to a successful multimodal therapy of chronic pain [2].

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L-2

The endocannabinoidome-gut microbiome axis

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For several decades, and starting some 25 years from its discovery, the only plant cannabinoid with an established mechanism for its pharmacological actions has been Δ^9-tetrahydrocannabinol (THC). To THC are ascribed the most important euphoric and psychotropic effects of recreational preparations (e.g. marijuana, hashish) obtained from those varieties of *Cannabis sativa* that are rich in this compound. The discovery of two G-protein-coupled receptors (GPCRs), the cannabinoid CB1 and CB2 receptors, specific THC led to the identification of their endogenous agonists, later named endocannabinoids: *N*-arachidonoyl-ethanolamine (anandamide) and 2-arachidonoyl-glycerol (2-AG). The chemical signaling system composed of CB1 and CB2 receptors, the two endocannabinoids and the anabolic and catabolic enzymes regulating endocannabinoid levels, became known as *the endocannabinoid system*. Later, an *expanded* endocannabinoid system, including several non-endocannabinoid long chain fatty acid amides and esters, among which: a) the congeners of anandamide and 2-AG, b) the *N*-acyl-aminoacids, c) the *N*-acyl-neurotransmitters and d) the primary fatty acid amides, has been discovered. These lipid mediators often share with the two endocannabinoids biosynthetic and/or inactivating enzymes, but not necessarily their receptors, which instead include orphan GPCRs, ligand-activated ion channels and peroxisome proliferator-activated nuclear receptors (PPARs). These small molecules, therefore, should not be considered endocannabinoids *sensu stricto*, but instead as endocannabinoid-like mediators, and this expanded endocannabinoid system is becoming known as the *endocannabinoidome* [1]. The endocannabinoidome is involved in almost all aspects of mammalian physiology and pathology, and recent work from my and other laboratories have highlighted how this complex signalling system is directly modulated by, and in turn modulates, another fundamental player in several physiopathological conditions: the gut microbiome [2,3]. I will present data on this endocannabinoidome-gut microbiome axis and its emerging role in obesity and neuropsychiatric and muscular disorders.

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L-3

Pharmacokinetics, interactions

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Introduction: Benefits of cannabidiol (CBD) in chronic pain treatment have been reported. However, as CBD is used as add-on therapy, the occurrence of pharmacokinetic drug-drug interactions (DDIs) between CBD and co-administered medications seems plausible. CBD is extensively metabolized in the liver and intestine mainly by cytochrome P450 enzymes and it also undergoes direct conjugation via UDP-glucuronosyltransferases (UGTs). CBD is not only a substrate but also an inhibitor and inducer of some CYP450 enzymes and an inhibitor of UGTs. Recently inhibition of carboxylesterases (CES) by CBD has also been reported. Pharmacokinetic DDIs between CBD for chronic pain and cyclosporine (CsA) and mychophenolate mofetil (MMF) as immunosuppressants in a kidney transplant patient were assessed. **Methods:** Close monitoring of the patient was performed with clinical control and laboratory data. Determination of CsA concentrations in whole blood samples was performed using CMIA Architect®, Abbot Laboratories. A LC-MS/MS method was developed and validated for the determination of CBD and a validated HPLC-UV method was used for quantification of mycophenolic acid (MPA), active metabolite of MMF. **Results:** A 50-year-old kidney transplant male patient was managed with 125 mg of CsA, 2000 mg of MMF and 5 mg of prednisone daily. Sublingual administration of CBD oil was started (1.6 mg/kg/day) and a great difference in CBD levels was observed. CsA concentrations decreased after CBD introduction, thus dose adjustment to 200 mg daily was needed. When CBD was then given orally with high-fat foods, CBD levels remain stable. MPA levels dropped during CBD treatment but with values within the therapeutic range reported in the literature (1.0-3.5 mg/L). After 2 months under CBD therapy, no improvement in pain management was observed and CBD was discontinued. After CBD discontinuation, MPA concentration rose. No toxic effects or transplant rejection were observed in the patient. **Conclusions:** Possible induction of CYP3A4 and inhibition of CES can explain the drop in CsA and MPA levels respectively. This study supports the need for implementing routine therapeutic drug monitoring to make dosage adjustments. Based on our findings, oral administration of CBD oil accompanied with high-fat foods resulted in less variable concentrations.
Keywords: Cannabidiol, immunosuppressants, pharmacokinetic interactions.

L-4

Cannabis dosing strategies for clinical success

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Introduction: As a medicine, cannabis is not only versatile in the conditions for which it can provide potential benefits, but in the ways in which it can be administered. Phytochemical composition, routes of delivery, formulation, dosage, and frequency of administration vary widely among patients. This complexity can be overwhelming for patients and clinicians, but provides a remarkable capacity for individualized treatment protocols that maximize therapeutic effects and minimize adverse effects. Clinical trials may fail to accurately measure the potential risks and benefits of treatment with cannabis by omitting the individualization that typically occurs in clinical practice. **Aims:** Provide a clear and concise description of the clinical strategies used by one clinician who is in close contact with cannabis clinician colleagues and recent educational content related to treatment with cannabis. **Methods:** Review the safe and effective dosing range of cannabinoids, nonlinear dose-response effects, dosing strategies for cannabis-naïve patients, reversing cannabis tolerance, current use of cannabinoid acids and cannabigerol (CBG), and the utility of various types of cannabis products and routes of administration. **Results:** Cannabinoids have a 5,000-fold dosage range in clinical practice and often follow a multiphasic dose-response relationship within that range. Cannabis-naïve patients can benefit from strategies that widen the therapeutic window and limit psychoactive adverse effects, while many patients benefit from therapeutic psychoactive effects. Appropriately-dosed cannabis typically does not lead to tolerance, and tolerance can be reversed with a short period of abstinence. Delivery methods that offer varying onset, duration, and therapeutic effects are commonly used in combination for optimal results. Clinicians are observing increasing use of cannabinoid acids as alternatives or adjuncts to their decarboxylated counterparts and the use of CBG-dominant preparations is becoming more common. **Conclusions:** With an understanding of the basic principles of cannabis dosing, treatments can be highly individualized to provide maximal benefit with minimal adverse effects. **Keywords:** Clinical, dosing, delivery, tolerance, psychoactivity.

L-5

Pharmacokinetics, psychtropic effects, and safety profile of a novel nanoparticle-based cannabinoid drug for oromucosal delivery

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Introduction: A phase-I, open-label clinical trial in healthy male subjects was conducted to assess the pharmacokinetic and safety profile of an oromucosal cannabinoid spray (AP701) containing a lipid-based nanoparticular drug formulation standardized to Δ-9-tetrahydrocannabinol (THC). **Methods:** Twelve healthy male subjects received a single dose of AP701 (12 sprays) containing 3.96 mg THC. Plasma samples were drawn 10 min-30 h post dose for analysis of THC and the active metabolite 11-hydroxy-Δ-9-THC (11-OH-THC). **Results:** The single dose of the applied oromucosal cannabinoid spray AP701 (12 sprays, 3.96 mg THC) resulted in a mean maximum plasma concentration (Cmax) of 2.23 ng/mL (90% CI 1.22-3.24) and a mean overall exposure (area under the concentration-time curve from time 0 to last measurable concentration [AUC0-t]) of 7.74 h × ng/mL (90% CI 5.03-10.45) for THC. For the active metabolite 11-OH-THC, a Cmax of 2.09 mg/mL (90% CI 1.50-2.68) and AUC0-t of 10.4 h × ng/mL (90% CI 7.03-13.77) was found. The oromucosal cannabinoid spray AP701 caused only minor psychotropic effects despite the relatively high dosage applied by healthy subjects. No serious adverse effects occurred. Overall, the oromucosal cannabinoid spray AP701 was well tolerated. **Conclusion:** Compared to currently available drugs on the market, higher AUC values could be detected for the oromucosal cannabinoid spray AP701 despite administration of a lower dose. These comparatively higher blood levels caused only minor psychotropic adverse effects. The oromucosal cannabinoid spray AP701 was well tolerated at a single dose of 3.96 mg THC. The oromucosal administration may provide an easily applicable and titratable drug formulation with a high safety and tolerability profile. **Keywords:** Cannabinoids, nanoparticles, oromucosal spray, pharmacokinetics, safety.

L-6

CBD and THC: Toxicity and overdose

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Introduction: Due to the increasing use of cannabinoids in the clinical practice and the increased adult use during the past years, it is important to review the literature regarding the preclinical, clinical evidence, scientific publications around toxicity, overdose and intoxication caused by cannabinoids. Since THC potency has increased over the past 20 years from around 4% to 20%, more adverse effects have been noted. Awareness among clinicians in how to manage intoxication and overdose in patients and to understand safety profiles of cannabinoid therapies is necessary. **Methods:** Searching the following databases PubMed, Google Scholar, The Cochrane Library; looking for the preclinical, clinical studies, scientific publications about the topics cannabinoid toxicity, CBD and THC toxicity, intoxication, and overdose with cannabinoids. **Results and Conclusions:** No deaths in rats and monkeys were observed given daily oral doses of 25 to 300 mg/kg of CBD for 90 days. CBD LD50 values after single IV doses of CBD were 50 mg/kg in mice. In humans the mean CBD dose of 22.9 mg/kg/day, increased up to 50 mg/kg/day CBD over a 12-week period resulted in mild and transient adverse events in most patients, with a small percentage of patients reporting serious adverse events. Dogs and monkeys can tolerate significantly higher oral doses of THC 3'000 mg/kg. THC LD50 values for rats administered single oral doses of THC, are approximately 1'000 mg/kg. The lethal dose of THC in humans has been extrapolated to be >15'000 mg. Conversion to an average inhaled dose of 7'350 mg and an average oral dose of 31'500 mg THC. Overdose with THC can cause dose-dependent and potentially significant mental and physical effects. Greater THC intoxication has been observed due to increased concentrations of THC in plants, resulting in more visits to the emergency room. It is important to educate doctors about treatment alternatives for cannabinoid intoxication and to conduct more research evaluating overdose and toxicity profiles of cannabinoids. **Keywords:** Cannabis, cannabinoids, CBD, THC, toxicity, overdose.

L-7

Transmucosal delivery of cannabidiol using vestibular electroporation in patients with vestibulodynia: interim analysis of a randomized, blinded prospective trial

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Introduction: Vulvodynia is a highly prevalent form of chronic genital pain in women. Localized provoked vulvodynia at the vestibule, known as vestibulodynia (VBD), is the most common subtype (about 80%). Women with VBD often describe vulvar pain as a burning, irritation, rawness, and dyspareunia (difficult or painful intercourse). The pattern of VBD responses is suggestive of sensory abnormalities in the form of evoked pain suggesting sensitization, an underlying manifestation of neuropathic pain. Furthermore, VBD is always associated with pelvic floor muscle overactivity. A multifactorial etiology, such as infections, hormone disorders, neuroinflammation, gene polymorphisms that interfere with inflammation have been implicated in the development and maintenance of VBD. There is no standard treatment of the disease, and few randomized controlled trials have been performed. **Aims:** To document the efficacy and safety of transmucosal delivery of cannabidiol (CBD) using vestibular electroporation in patients with VBD. The abundant distribution of cannabinoid receptors on skin nerve fibers provides implications for its anti-inflammatory, anti-nociceptive action and anti-neuropathic therapeutic potential. **Methods:** A total of 60 patients with VBD were randomly divided into two equal groups: transmucosal delivery of 3 mL CBD 8% gel (active group) or 3 mL gel (placebo group) using vestibular electroporation. Each patient received 6 weekly treatments with a follow-up after 1 and 2 months. The outcomes were: 0–10-point visual scale (VAS) related to dyspareunia and vulvovaginal pain; assessment of current perception threshold testing using the Neurometer CPT/C and vaginal electromyographic measurements. We conducted an interim analysis after 24 patients (15 in active group and 9 in placebo group) have completed the one-month follow-up. **Results:** All the variables involved improved after the treatment in the CBD group (pain from 6.4 to 4.6, $p < 0.05$; dyspareunia from 7.6 to 4.3, $p < 0.05$; muscular tone from 5.0 to 3.6, $p < 0.05$; neurometer parameters: 2000 Hz from 346 to 447; 250 Hz from 156 to 197; 5 Hz from 50 to 84- $p < 0.05$). While in the placebo group they have little changes. No relevant side effects were reported in both groups (transient burn after treatment). **Conclusions:** Interim analysis of this trial demonstrated that our treatment was safe and effective. **Keywords:** CBD, pelvic pain hyperalgesia, vulvodynia, vestibulodynia. **Acknowledgements:** The CBD gel was provided by Curaleaf International Pharma.

L-8

Is medical cannabis use associated with improved sleep in PTSD patients? A diary study

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Introduction: Despite an increase in use of medical cannabis (MC) among PTSD patients, there is a lack of research on the therapeutic effects of MC in the treatment of PTSD symptoms. Within the limited literature, evidence suggests that cannabinoids may decrease PTSD symptomology, in particular sleep disturbances. **Aims:** This study examines the time elapsed between cannabis use and sleep onset and its association with the following main indicators of sleep disturbances related to PTSD symptoms: (1) number

of awakenings throughout the night, (2) early awakenings, (3) nightmares. **Methods:** Each morning over a 2- to 3-week period, 77 PTSD patients reported on the timing of previous night MC use and sleep disturbances via their smartphone/ computer. Mixed effects models examined within-person variation regarding time elapsed between previous night MC use, sleep onset and sleep disturbances. **Results:** Within-person analyses found that shorter time gaps between previous night MC use and sleep start time was associated with lower likelihood of experiencing nightmares throughout the night, but it was not associated with nightly awakenings or waking up too early. Between-person analyses showed that individuals who used MC products with higher CBD concentrations reported fewer early awakenings. **Conclusion:** MC use prior to sleep may help prevent nightmares and high CBD products may be instrumental in preventing early awakenings. These preliminary results indicate that future research should test causal relations between MC use and sleep problems in PTSD patients. Future research is warranted in order to explore causal relationships between MC use, nightmares and insomnia in PTSD patients. **Keywords:** Daily diary study, insomnia, medical cannabis, nightmares, PTSD. **Acknowledgements:** The authors would like to thank the respondents who participated in the study.

L-9

Cannabinoids in the treatment of movement disorders

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Introduction: It is well established that the basal ganglia are involved in the regulation of motor function through the cortico–basal ganglia–thalamo–cortical loops. Accordingly, it is believed that hyper- as well as hypokinetic movement disorders are related to a dysfunction in these circuits. For many years, it is also known that the endogenous cannabinoid system (ECS) is involved in neural signaling within the basal ganglia. In addition, cannabinoid CB1 and CB2 receptors are densely located in the basal ganglia circuits including the striatum, substantia nigra, and globus pallidus. CB1 receptors are expressed in glutamatergic and gamma-aminobutyric acid (GABA)-ergic neurons projecting to the striatum. Both CB1 and CB2 receptors also interact with dopaminergic signals. This complex interaction of the endocannabinoid signaling with other important neurotransmitter systems in the basal ganglia suggests on the one hand that the ECS plays a key role in the pathophysiology of different movement disorders and on the other hand that cannabinoids may represent a new treatment strategy for these disorders. **Aims:** To give a comprehensive overview about current clinical data on the effectiveness of cannabinoids in the treatmnent of hyop- and hyperkinetic movement disorders. **Methods and Results:** In the first part of the presentation, a summary will be given about available data using cannabinoids in the treatment of movement disorders including Parkinson's disease, tremor, Huntington's disease, and dystonia. In the second part, new data will be presented using the cannabinoid extract nabiximols in the treatment of tics in patients with Tourette syndrome. **Conclusions:** Although endocannabinoids are heavily involved in cortico–basal ganglia–thalamo–cortical loops and complexly interact with several other neurotransmitters, it is still unclear, whether movement disorders are caused by a dysfunction in the ECS. While cannabinoids are regarded as a third choice treatment in tics in patients with Tourette syndrome, in all other movement disorders the database is still very weak and no final conclusions can be drawn. **Keywords:** Cannabinoids, tetrahydrocannabinol, cannabidiol, movement disorders, tics.

L-10

Migraine, headache

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Cannabinoids, mainly CBD and THC, have a very long history in medicinal use and - following a long social and legal ban – reemerged into the clinical reality world wide. A broad range of neurological disesases and conditions have been treated with cannabinoids but only a few of them also been studied scientifically. For migraines and all other headaches cannaboids have been used, but no double blind trial has been performed, nor for migraines or other headaches. Therefore clinical evidence of the treatment at Hirslanden Headache Center will be reported and discussed. Also the hurdles for state of the art trials.

L-11

Paediatric pain and palliative care

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Introduction: Pain is a difficult and distressing symptom in children suffering from life-limiting illnesses. For these children (0-18 years of age) diagnoses range from neurological diseases to advanced heart disease and cancer. As an overwhelming proportion of children with palliative care needs have neurological conditions with cognitive impairment, the recognition of pain is an important task for clinicians. Regardless of the underlying disease, pain treatment for children combines pharmacological with non-pharmacological therapies, just as it does in adults. Treatment must be adapted to the individual situation and needs of the child and always includes the perspective of the parents and the family ("unit of care"). This presentation will highlight the different pharmacological strategies of pain treatment in children suffering from a variety of conditions and will also addresses the experiences of using cannabinoids in these children. **Results:** Pain occurs in 70% to over 90% of children who need palliative care. However, pain is particularly prone to underdiagnosis and inadequate or suboptimal treatment. Since self-assessment is not possible for most of these children, the Faces, Legs, Activity, Cry and Consolability scale (FLACC)/FLACC-Revised is recommended as an observational tool and can improve the recognition of pain in verbally non-communicative children. Many children will require opioids during the course of their illness and a large proportion will benefit

from cannabinoids alongside other co-analgesics, such as gabapentin, clonidine and others. **Conclusion:** The treatment of pain is a cornerstone of palliative care, but also of medicine in general. The aim of palliative care is to improve the quality of life, which cannot be achievable if pain does not receive the necessary attention. The individuality of the child and the preferences of the family must also be taken into account. **Keywords:** Paediatric palliative care, pain, assessment and treatment of pain.

L-12

Meeting the needs of geriatric and palliative care patients through cannabinoid-based medicines

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Introduction: Cannabis use has been accelerating at a faster pace in older adults than among other age groups. It is estimated that 400,000 older Canadian adults reported using cannabis in the past three months [1]. Cannabinoid-based medicines (CBM) have also seen an increased interest and uptake by palliative care patients, who use these medicines to treat a wide variety of symptoms [2]. It is therefore essential to understand older adults, geriatric and palliative care clinicians expectations with respect to the role CBM may play for these patient populations. **Aims:** To describe older adults, clinicians and palliative care physicians perceptions with respect to CBM use in geriatric medicine and palliative care settings. **Methods:** The Canadian Coalition for Seniors' Mental Health (CCSMH) conducted a survey needs assessment to understand clinician's and older adults experiences and perceptions regarding cannabis use in aging. Focus groups with palliative care clinicians from 3 latinamerican countries were conducted to solicit opinions on CBM clinical utility, safety, and research needs. **Results:** The CCSMH survey revealed that while 89% of physicians are aware of older adults in their practice using cannabis, only 39% of physicians felt that they had sufficient knowledge to address older patients' questions about cannabis. Pain, anxiety, and sleep issues are the most common reasons older adults report using cannabis. Similarly, latinamerican palliative care clinicians reported that CBM are suited to treat pain, anxiety, sleep concerns, and end of life distress. Latinamerican palliative care clinicians held positive views with regard to the safety of CBM, satisfactory clinical outcomes when these medicines were used under medical supervision, and considered medication interactions are a top research priority. **Conclusions:** Although cannabis use is common among older adults, a significant proportion of clinicians still report insufficient knowledge to address older adults' cannabis related queries. Latinamerican palliative care clinicians believe CBM, when used as adjunct to other medicines, may help achieve adequate symptom control and alleviate end-of-life distress. These viewpoints are important to target education efforts, and justify continuing expanding the evidence-base on efficacy, comparative effectiveness and medication interactions. **Keywords:** Geriatric medicine, palliative care, clinician perceptions, end of life. **Acknowledgements:** I'd like to thank CAMEDA - Cannabis Medicinal Argentina for their support and contributions to the focus group project.

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L-13

ADHD and autism, an overview

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Autism Spectrum Disorder (ASD) and Attention Deficit Hyperactivity Disorder (ADHD) are heterogeneous clusters of neurodevelopmental disorders. The estimated average prevalence of ASD ranges between 0.5% and 1.5%. ADHD affects around 5% of children and 3% of adults. Whereas in ASD conventional psychopharmacological treatment such as atypical antipsychotics, selective serotonin reuptake inhibitors, stimulants and anxiolytics is used to mitigate inappropriate behaviors, and no pharmacological intervention is known to address core symptoms, there is a range of specific medication such as stimulants, norepinephrine reuptake inhibitors and guanfacine used in the treatment of ADHD that has proved to be effective in treating core symptoms of the disorder. According to preclinical trials and animal models, signaling in the endocannabinoid system, with effects on levels of glutamate, glutamine and GABA and on the dopamine system may play a role in the manifestation of both disorders, possible hypotheses are discussed. Cannabinoids are widely used on an individual, off-label basis for the treatment of ASD and ADHD and there is anecdotal evidence for the medical use of cannabinoids in ADHD and ASD. But as of yet there is a scarcety of reliable data coming from clinical studies. Existing data are presented with methodological limitations that are inherent in the research field, which are blinding, lack of control group, heterogeneity of the administered cannabinoids, heterogeneity of outcome measures and lack of statistcal power. Altogether promising effects of cannabinoids on core symptoms and accessory symptoms of ASD and ADHD could be provided in the existing data so far. To corroborate these findings on the effects of cannabinoids, and to get more data on tolerability and safety, randomized, double-blind and placebo-controlled clinical trials, as well as longitudinal studies, are necessary.

L-14

Cannabis-based medicine in psychiatry: promising new treatment strategies or snake oil?

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In the past decades, THC-rich cannabis preparations (marijuana, hashish) have been considered as harmful substances exclusively in regard to health damage in psychiatry, for example as a cause of a psychosis and drug addiction. Furthermore, cannabis was considered as a gateway drug for harder drugs. These views still have an impact on the training of psychiatrists and neurologists, as well as on the image of the role of cannabis in the context of psychiatry. Although causality and the extent of causality are controversially discussed, it is generally accepted that cannabis use disorders is associated with a variety of mental disorders including schizophrenia, anxiety disorders, depression and attention-deficit/hyperactivity disorder (ADHD). For this reason, psychiatric disorders, more or less regardless of the type of disorder, have been and in many cases are still considered as absolute contraindications with respect to therapy with cannabis-based medications. However, over the past 20 years, basic research, case reports, small-scale studies, and experience in the therapeutic use of cannabis-based medicines have demonstrated that both THC- and CBD-rich cannabis preparations may be of benefit in a number of patients suffering from a variety of different psychiatric disorders. Psychiatric and neuropsychiatric conditions, where THC-rich preparations may be of benefit, include neurodevelopmental disorders such as Tourette syndrome and other tic disorders, ADHD, autism spectrum disorder (ASD), obsessive-compulsive disorder, depression, anxiety disorders, sleep disorders, post-traumatic stress disorder (PTSD), borderline-type personality disorder, bipolar disorder, and addictive disorders, but also behavioral problems in neurodegenerative disorders such as Alzheimer's disease. There have even single cases been reported where THC-rich cannabis medications had been of benefit in patients with schizophrenic psychosis. On the other hand, there is increasingly robust data suggesting that CBD-rich cannabis preparations might be effective in psychiatric conditions such as schizophrenic psychosis, anxiety disorders, depression, addiction disorders, sleep disorders, and ASD. While the use of CBD-containing medications is relatively well accepted among psychiatrists and neurologists - especially since it acts as an allosteric modulator at the CB1 receptor to counteract the psychedelic and thus psychosis-promoting effects of THC - the use of THC-containing medications continues to meet with traditional skepticism among psychiatrists. **Keywords:** Cannabis, THC, CBD, psychiatry, schizophrenia.

L-15

Cannabidiol for COVID-19 patients with mild to moderate symptoms (CANDIDATE Study): A randomized, double-blind, placebo-controlled clinical trial

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Introduction: Owing to its anti-inflammatory properties and antiviral *"in vitro"* effect against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), cannabidiol (CBD) has been proposed as a potential treatment for coronavirus disease 2019 (COVID-19). **Aims:** To investigate the safety and efficacy of CBD for treating patients with mild to moderate COVID-19. **Method:** Randomized, parallel-group, double-blind, placebo-controlled clinical trial conducted between July 7 and October 16, 2020, in two sites in Brazil. Patients were recruited in an emergency room. Block randomized patients (1:1 allocation ratio-by a researcher not directly involved in data collection) with mild and moderate COVID-19 living in Ribeirão Preto, Brazil, seeking medical consultation, and those who voluntarily agreed to participate in the study. Patients received 300 mg of CBD or placebo added

to standard symptomatic care during 14 days. The primary outcome was reduction or prevention of the deterioration in clinical status from mild/moderate to severe/critical measured with the COVID-19 Scale or the natural course of the resolution of typical clinical symptoms. Primary study outcome was assessed on days 14, 21, and 28 after enrollment. **Results:** A total of 321 patients were recruited and assessed for eligibility, and 105 were randomly allocated either in CBD (n = 49) or in placebo (n = 42) group. Ninety-one participants were included in the analysis of efficacy. There were no baseline between-group differences regarding disease severity ($x^2 = 0.025$, $p = 0.988$) and median time to symptom resolution (12 days [95% confidence interval, CI, 6.5-17.5] in the CBD group, 9 days [95% CI, 4.8-13.2] in the placebo group [$x^2 = 1.6$, $p = 0.205$ by log-rank test]). By day 28, 83.3% in the CBD group and 90.2% in the placebo group had resolved symptoms. There were no between-group differences on secondary measures. CBD was well tolerated, producing mostly mild and transient side effects (e.g., somnolence, fatigue, changes in appetite, lethargy, nausea, diarrhea, and fever), with no significant differences between CBD and placebo treatment groups. **Conclusions and Relevance:** Daily administration of 300 mg CBD for 14 days failed to alter the clinical evolution of COVID-19. Further trials should explore the therapeutic effect of CBD in patients with severe COVID-19, possibly trying higher doses than the used in our study. Trial Registration: ClinicalTrials.gov identifier http://clinicaltrials.gov/show/NCT04467918 (date of registration: July 13, 2020). **Keywords:** COVID-19, SARS-CoV-2, cannabidiol, clinical trial, infectious diseases, internal medicine.

L-16

Cannabis in inflammatory bowel disease: Past, present and future

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Inflammatory bowel diseases (IBDs) are chronic, idiopathic, inflammatory gastrointestinal disorders. Many experiments in cellular as well as animal models demonstrated a benefit in cannabis treatment. In experimental models of colitis in rodents, treatment with cannabinoids reduced colon injury, inducible nitric oxide synthase, myeloperoxidase activity and colonic motility. It also normalized levels of IL1B, IL10, and interferon gamma. Treatment of biopsies from ulcerative colitis colons affected eCB "tone". Retrospective studies have shown a clinical benefit in cannabis treatment. A retrospective, observational study of 30 patients demonstrated reduction of disease activity index ($p < 0.001$) and of the need for other medication. Patients using cannabis for their IBD reported reduced abdominal pain (83.9%), abdominal cramping (76.8%), joint pain (48.2%), and diarrhea (28.6%). Data from a national in-patient sample of Crohn's disease patients demonstrated that cannabis users had significantly less active fistulizing disease, intra-abdominal abscess, blood transfusion, colectomy, and parenteral nutrition. In 9 patients with pouchitis, symptoms and quality of life were significantly improved by cannabis treatment. Few randomized controlled studies regarding cannabis treatment in IBD were performed. In one trial, 21 patients with active Crohn's Disease were given either cannabis or placebo. Complete remission (CDAI score 100 points) was observed in 5 of 11 subjects in the cannabis group, 5 and 4 of 10 in the placebo group (p=0.43). A randomized trial evaluated the effects of low-dose (10 mg) CBD vs placebo in 19 patients for 8 weeks failed to show a difference in CDAI scores at the end of the study. A randomized trial of 50 patients with active Crohn's disease comparing cannabis oil (CBD/THC 4:1) to placebo resulted in a significantly lower CDAI in the cannabis treated group ($p < 0.05$). In a study with a CBD-rich cannabis extract on ulcerative colitis patients, remission rates at the end were similar in both study and placebo groups. Another study in 30 active ulcerative colitis patients demonstrated a significantly lower disease activity index in the cannabis treated group at the end of the study (p=0.001). **Conclusion:** Further studies of the use of cannabis and its derivatives could lead to new therapeutic avenues in the treatment of IBD.

L-17

Cannabidiol in gynecology focussing on pre- and postmenopausal complaints

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Menopause symptoms often begin around the 45th year of life and usually last up to the 65th year of life. A distinction is made between vegetative, psychological and organic menopausal syndrome. Cannabidiol (CBD) might be useful for a number of symptoms, either alone or in combination with other herbal or synthetic drugs, and is successful in achieving an improved quality of life for women suffering of menopause sympotoms. Experiences with phytocannabinoid therapy in a gynecological practice are reported. Treatment outcomes for vulvovaginal atrophy with local and intravaginal cannabinoid application will also be presented.

L-18

The endocannabinoid system as a therapeutic target and patient screening tool in breast cancer

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Our group recently described the physical interaction between cannabinoid receptor 2 (CB2R) and the receptor tyrosine kinase HER2, one of the main drivers of the breast cancer subtype known as HER2-positive. The resulting complexes trigger the pro-oncogenic activity of HER2, and when disrupted, shift cancer cell signaling towards antitumoral responses. Here, evidence will be presented showing 1) that HER2-CB_2R heteromer disruption by cannabinoids is a new therapeutic strategy to prevent breast cancer progression and 2) that the expression of these complexes in human tumors correlates with patient prognosis and responsiveness to anti-HER2 therapy. Our results therefore point to HER2-CB_2R heteromers as new therapeutic targets and patient screening tools in HER2+ breast cancer.

L-19

Medicinal use of different cannabis strains: results from a large prospective survey in Germany

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Introduction: Up to know it is unclear whether different medicinal cannabis (MC) strains are differently efficacious in different medical conditions. **Aims:** To compare effictiveness of different MC strains depending on the disease to be treated. **Methods:** This study was conducted as an online survey in Germany between June 2020 and August 2020. Patients were allowed to participate only if they received a cannabis-based treatment from pharmacies in form of cannabis flowers prescribed by a physician. **Results:** Altogether, 1,028 participants completed the survey. The majority of participants had experience with MC that lasted longer than one year (58%). At the time of the survey, a total of 43 MC strains could be precribed among them 34 (76%) delta-9-tetrahydrocannabinol (THC)-dominant strains, 3 (7%) cannabidiol (CBD)-dominant strains and 6 (13%) with balanced THC/CBD ratio. „Bedrocan" was the most frequently precribed strain followed by „Bakerstreet" and „Pedanios" 22/1. On average, participants stated that they have used 5.9 different strains. The taste/smell was predominantly perceived as good or very good (n=730, 71.1%). On the other hand, when considering the prize:effectiveness ratio, it was mainly rated as medium (23%), poor (20%) or very poor (21%). The costs of the therapy were fully or partially covered by the health insurence for only 398 participants (38.7%). The most frequent conditions MC was prescribed for were pain disorders, various psychiatric and neurological diseases, and gastrointestinal symptoms. Overall, the mean patient-reported efficacy was 80.1%. The most highly rated MC strains were „Bedrocan", „Bakerstreet" and „Pedanios" 18/1. Using a regression model testing an association between patient-reported efficacy and MC strain, however, no association between the patient-reported efficacy and the variety could be found. Furthermore, no influence of the disease on the choice of the variety was measurable. On average 2.1 side effects per person were reported, the most common were dry mouth (19.5%), increased appetite (17.1%), and tiredness (13.0%). However, 29% of participants did not report any side effects. **Conclusions:** Patients' self-reported efficacy and tolerability of MC was very good. We found no evidence suggestiong that specific MC strains are superior depeding on the disease to be treated. One of the important limitations of our study is that it was conducted two years ago and, therefore, results concerning cannabis strains would have been different today. **Keywords:** Medicinal cannabis, tetrahydrocannabinol, cannabidiol, patient's experience, side effects.

L-20

Preparation of a placebo-controlled trial of THC-CBD medication for severely demented patients with behavioral symptoms: a marathon full of barriers and pitfalls

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Introduction: The medical use of cannabinoids is the subject of growing interest for various indications, even if scientific evidence to guide prescription is often lacking, especially in the elderly, frequently neglected in clinical research. In an observational study in Geneva (Switzerland), we found that administering a standardized THC/CBD oil was feasible, safe, and beneficial in an elderly polymedicated population with severe dementia, behavioral troubles, and rigidity. To prove the efficacy of cannabinoids in the management of rigidity, behavioral symptoms, or pain in patients with severe dementia, we decided to set up a randomized clinical trial (RCT). **Aims:** This work aims to present the barriers and pitfalls in preparing the RCT to help other researchers anticipate some of the difficulties. **Methods and Results:** We designed a randomized, multicenter, double-blind, placebo-controlled cross-over study in patients who are permanent nursing facility residents. The study treatment is a standardized THC/CBD (1:2) oil. The preparation started in May 2021. The obstacles we encountered were multiple, hindering the developing time and requiring substantial planning, experience, and motivation: – Lack of previous studies and literature; – Vulnerable population - consent must come from legal representatives; – Medication - not a recognized drug by Swissmedic (Swiss Agency for Therapeutic Products; – Placebo - same color and taste but no active ingredients ; – Delicate choice of the medication producer avoiding conflicts of interest; – Study drug supply and control; – High budget - medication, management, safety, and insurance issues; – The subtlety of different study settings (facilities untrained in clinical trials); – Ethic issues that all this implies. After 15 months, we received ethical approval and are now waiting for Swissmedic approval. This came after days of discussions, remodeling, and adapting, and was only possible thanks to the excellent cooperation of highly determined key figures, as well as the appointment of a study coordinator. **Conclusions:** Designing and setting up a RCT is always challenging but a clinical trial on medical cannabis must face additional issues related to the dynamic to complete the efficacy and safety profiles and the status of cannabis. Still, the scientific community needs such trials, and it is crucial to perseverate in the effort. **Keywords:** Cannabinoids, medical cannabis, THC/CBD oil, clinical trials.

L-21

Controlled inhalation of THC-predominant cannabis flos improves health-related quality of life and symptoms of chronic pain and anxiety in eligible UK patients

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Introduction: In November 2018, the UK's Home Office established a legal route for eligible patients to be prescribed cannabis-based products for medicinal use in humans (CBPMs) as unlicensed medicines. These include liquid cannabis extracts for oral administration («oils») and dried flowers for inhalation («flos»). Smoking of CBPMs is expressly prohibited. To date, THC-predominant cannabis flowers remain the most prescribed CBPMs in project Twenty21 (T21), the first multi-center, prospective, observational UK cannabis patient registry. **Aims:** To investigate the effect of chemotype I (THC-predominant) cannabis flos controlled inhalation on health-related quality of life (HRQoL) and clinical symptoms in a treatment-resistant population of patients diagnosed with chronic painful conditions and anxiety-related disorders. **Methods:** We analyzed patient-reported outcome measures (PROMS) collected prospectively from T21 patients prescribed with THC-predominant flos Khiron 20/1, the most-frequently prescribed CBPM in the project. An administration protocol by means of a certified medical device was recommended for all participants (panel A). PROMS collected at baseline and at subsequent 3- and 6-months follow-ups included health-related quality of life (HRQoL), general mood, and sleep, as well as condition-specific measures of illness severity (panel B). **Results:** Participants (N=191) were mostly males (76.9%, average age = 39.4) diagnosed mainly with chronic pain (57.6%) and anxiety-related disorders (25.6%). Inhalation of Khiron 20/1 was associated with a marked increase in self-reported HRQoL, general mood, and sleep (N=191; $P<0.001$). Condition-specific assessments showed marked improvements in both pain severity (T=5.33; $P<0.001$) and pain interference (T=6.31; $P<0.001$) in patients using Khiron 20/1 for chronic pain (N=109). Similar results were found for patients diagnosed with anxiety-related disorders (N=54; T=10.4; $P<0.001$). These clinical outcomes were maintained at the 6-months follow up (N=63; $P<0.001$) (panel C). Only one participant (<1%) reported a side effect associated to the treatment (memory loss). **Conclusions:** Our results indicate that controlled inhalation of pharmaceutical grade, THC-predominant cannabis flos is associated with a significant improvement in patient-reported pain scores, mood, anxiety, sleep disturbances and overall HRQoL in a treatment-resistant clinical population. **Keywords:** Chronic pain, anxiety, inhalation, tetrahydrocannabinol, HRQoL.

L-22

The dark side of cannabidiol: The unanticipated social and clinical implications of synthetic delta-8-THC

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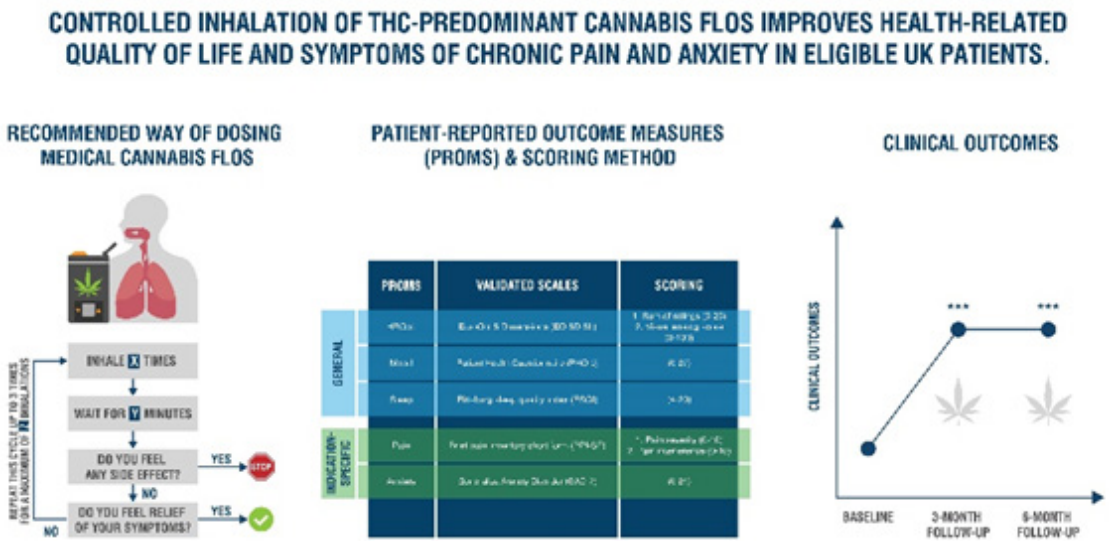
Introduction: The explosive growth of the cannabis industry in the United States over the past decade has spurred a multitude of products derived from phytocannabinoids produced by *Cannabis sativa* L. Decades of federal misguidance and cannabis prohibition has caused cannabis policy missteps that have created enormous and unanticipated issues. Here we consider how the 2018 Farm Bill, which essentially legalized cannabidiol (CBD) and all its derivatives, created an enormous market for a heretofore obscure



cannabinoid, Δ^8-THC. **Methods:** Herein, we review the available literature of the complexity of the chemistry of its current manufacture, namely, the acid-catalyzed ring closure of CBD (ACRCC), the myriad of issues involving the unsolved technical problems with quality control of ACRCC-Δ^8-THC and the multitude of isomerized byproducts, and the lack of consistent regulation regarding consumer safety and labeling. **Results:** We provide what we believe is the first comprehensive listing of all the documented ACRCC-Δ^8-THC byproducts. Perhaps most importantly, we highlight the growing concern that ACRCC-Δ^8-THC products, of which none, other than Δ^8-THC, have been subjected to any human toxicological evaluation. This is especially troubling as ACRCC-Δ^8-THC products relate to vaping, and their contribution to a growing and lethal epidemic of electronic cigarette, or vaping, product use–associated lung injury (EVALI). **Conclusions:** Quality control is totally inadequate in the newly emerging Δ^8-THC industry. American consumers are ingesting products that are mislabeled with many compounds that have never received any toxicological testing. EVALI cases continue to be reported with a fatality rate approaching 2% (in California). **Keywords:** CBD, Δ8-THC, ACRCC-Δ8-THC, by-products.

L-23

Dermatological case reports from a medical practice: From hyperhidrosis to basal cell carcinoma

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Introduction: The endocannabinoid system of the skin plays an important role in various biological processes, and has been suggested to be a promising target for a range of dermatological diseases, including acne, seborrhea, allergic dermatitis, itch, psoriasis, cancer, and hair follicle regression [1, 2]. However, so far no clinical study has been conducted in this area of research and only a few case reports have been published so far. **Presentation of Cases:** Four cases of different skin diseases from a medical practice are presented. All patients are Caucasians. A 41-years old man with hereditary hyperhidrosis experienced severe side effects from standard pharmacological treatment and developed compensatory sweating after endoscopic symphatectomy. He started to inhale cannabis in 2012, which stops sweating within a few minutes lasting for 2 to 3 hours. A 42-years old man with hidradenitis supportive had to undergo repeated surgery of abscesses in the perianal, perigenital and inguinal regions every year before he started to use cannabis in 2008. A 33-years old man suffers from psoriasis since 2001 and was treatment-resistant to standard medication, including corticoids, methotrexate and biologicals. Cannabis reduces inflammation, itching and associated scratching and improves sleep, quality of life and ability to work. A 74–years old man suffered from recurrent multifocal basal cell carcinomas on his nose. He underwent surgery in 2003 and after recurrence in 2016 applied a topical cannabis extract, which removed the carcinomas within two weeks. **Conclusion:** Many patients have detected that the use of cannabis may be helpful in their dermatological diseases. Doctors should be aware, that patients experiencing considerable improvement in these conditions by cannabis products may not be isolated cases, and that these experiences have a rationale biological basis. Dermatology is an underresearched, but promising area for the use of cannabis-based medicines. **Keywords:** Cannabis, hyperhidrosis, acne inversa, psoriasism basalioma.

References

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Are important just only cannabinoids?

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Discovery of the main cannabinoids (cannabidiolic acid, cannabidiol, Δ^9-tetrahydrocannabinol, cannabigerol) in Cannabis sativa L., cannabinoid receptors (CB1, CB2) and the main endocannabinoids (anandamide, 2-arachidonoyl glycerol) opened door to medical use of Cannabis sativa L. plant on the scientific level. These discoveries sparked interest in research, medicinal use, and ultimately business in this field. Research is currently moving forward by leaps and bounds. It is perhaps not possible for one person to read all scientific works on this topic. Nevertheless, we are still only at the beginning in the field of treatment due to restrictions and lack of knowledge. Only a few cannabinoids are currently used in cannabis treatment. However, it is clear that these substances do not fully explain the medicinal effect of cannabis. Different chemotypes of cannabis with the same quantitative content of cannabinoids affect the patient differently. Obviously, other substances which are important for treatment (terpenes, terpenoids, flavonoids, flavonoid glycosides, polyphenols or other substances) play a role here. It is necessary to pay due attention to this research so that the treatment (even if mostly only palliative) will be sufficiently successful. All the data from the doctor, the treated patients and the scientists can together lead to a successful goal.

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Research and development for new cannabis-based medical drugs for different medical indications: ovarian cancer in the spotlight

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Introduction: *Cannabis sativa* is widely used to alleviate numerous symptoms associated with medical conditions. Ovarian cancer (OC) is the most lethal gynecologic malignancy in the western world. Recently, it was demonstrated that phytocannabinoids have anticancer activity *in vitro* and *in vivo*. However, only a few studies have examined the effectivity of cannabis compounds against OC. **Aim:** To examine the effectiveness of combinations of cannabis compounds against OC. **Methods:** Cytotoxic activity was determined by XTT assay. Chemical composition was determined using high-performance liquid chromatography (HPLC) and gas chromatography mass spectrometry (GC/MS). Apoptosis and cell cycle were determined by fluorescence-activated cell sorting (FACS). Cell migration was determined by scratch assay. Gene expression was determined by quantitative PCR. In vivo experiments were performed on xenograft mice model. **Results:** The two most active fractions, F5 and F7, from a high Δ9–tetrahydro-cannabinol (THC) cannabis strain extract, and their standard mix (SM) showed cytotoxic activity against OC cells. The most effective phytocannabinoid combination was THC + cannabichromene (CBC) + cannabigerol (CBG). F5, F7 and SM affected cell cycle, led to cell apoptosis and to a marked reduction in cell migration. The cytotoxic activity was mediated via CB2 and TRPV2 receptors. These fractions act in synergy with niraparib, an inhibition of Poly (ADP-ribose) polymerase 1 (PARP1) inhibitor, and were ~50 fold more cytotoxic to OC cells than to normal keratenocytes. The niraparib+F7 treatment was effective on an OC patient's cells and in a xenograft mice model (Figure 1). The niraparib+F7 treatment reduced Wnt pathway gene expression. **Conclusions:** We identified cannabis compounds with substantial cytotoxic activity against OC cells, which involves cell cycle arrest and apoptosis. This activity was found to be mediated via CB2 and TRPV2 and to be considerably stronger on cancer cells than on normal cells. Synergistic activity was found between the cannabis extract fractions and niraparib in vitro. Treatments by F7 and/or niraparib led to alterations the canonical Wnt signaling pathway gene expression; Wnt pathway inhibition may increase sensitivity to PARP inhibitor in non-BRCA cells. Clinical trials with cannabis-based products are needed desperately for OC patients. **Keywords:** Ovarian cancer, cannabis, phytocannabinoids, apoptosis, Wnt pathway. **Acknowledgements:** Research was funded by Canna Onc Research.

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Serendipity, the prepared mind, and rejection (of the hypothesis)

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The identification of the cannabinoid receptors, the endocannabinoids, and the EndoCannabinoid System (ECS) that we know of today was not intuitively obvious based upon known prototypical cellular signaling mechanisms. Dr. Howlett entered the field of cannabinoid research when bioactive phytocannabinoid compounds were identified, but cellular mechanism(s) for their actions in animal models were unknown. The story began with the rejection of two hypotheses that (1) phytocannabinoids perturb neuronal function by disordering plasma membranes or (2) pain relief by Δ^9-tetrahydrocannabinol (THC) is due to competitive antagonism of prostaglandin receptors. The discovery of a cannabinoid receptor in the brain resulted from the interface between Dr. Howlett's academic research laboratory and the unpublished evidence that Pfizer Central Research scientists had accrued in their project to develop a novel analgesic based upon the active metabolite 11-OH-THC. As a result of the Pfizer decision to discontinue the cannabinoid analgesics project, a wealth of data could be published and tools could be developed for use by academic researchers. Identification of the brain (CB_1) and immune system (CB_2) cannabinoid receptors led to understanding of their localization, and cellular signaling mechanisms via Gi and other G proteins. The ability to identify the receptors allowed exploration of the mechanism(s) of phytocannabinoids, the identification of anandamide and 2-arachidonoylglycerol as endocannabinoids, the characterization of cannabinoid structural analogs (e.g. CP55940) and cannabimimetic indoles (e.g. WIN55212-2) as agonists, and the discovery of antagonists (SR141716, SR144528) from high-throughput screens of compounds. We now know that regulation of cellular signaling via cannabinoid receptors continues from phosphorylation and β-arrestin binding, desensitization and degradation. We also appreciate that CB_1 receptor interacts with other cellular proteins, such as the Cannabinoid Receptor Interacting Protein (CRIP1a) to regulate cellular functions potentially associated with the ECS role in neurotransmission. The progression of our current understanding of ECS physiology and pharmacology has resulted as much from serendipity in research findings, rejection of predicted hypotheses, and development and testing of novel alternative hypotheses, as it has from pre-planned research proposals. **Acknowledgements:** Howlett studies have been supported by NIH grants DA03690 and DA042157.