Medical Cannabis and Cannabinoids

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Abstracts

Congress Chairs:
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Medical Cannabis and Cannabinoids

P-01

Cannabis and Metals: Soils Need to be Controlled

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Background: Transition metals are well represented in mining regions, as in New Caledonia (NC) and could form reactive carbonyl species when burned.

Objective: To evaluate the toxicity of cannabis growing on ultramafic soils.

Methods: Metals of 49 NC cannabis flower heads samples from outdoor crops and soils from different NC sites were assayed by ICP-AES. Moreover, 500 mg of 4 NC cannabis samples underwent incomplete combustion for 10 min. Fumes were aspirated, cooled and condensed in a methanol bath. Ni, Co, Cr, Mn and Fe, condensation baths, tars, and methanol control solutions were assayed by ICP-MS.

Results: Heavy metals appear to passively enter cannabis. Depending on soil composition, we obtained four groups of cannabis:

High levels of Al group (maximum level (Lmax) 6780 μg/g of dry plant).

High levels of Ni and Co group (Lmax: 95 and 2 μg/g, respectively).

High levels of Cr, Ni and Co group (Lmax: 400, 620, 40 μg/g, respectively).

High levels of Mn group (Lmax: 14818 μg/g).

In NC cannabis, Fe levels are high when soils are rich in ferronickel (23910 μg/g). In addition, high levels of Pb, Cu and Os were observed (30, 124 and 45 μg/g, respectively). These metal levels are much higher than levels found in commercial tobaccos. Some NC cannabis samples have a Ni content nearly 500 times higher (620 μg/g) than these tobaccos. The following maximum quantities were trapped in the fumes by "bang" of 500 mg of cannabis: 360 ng of Ni, 2.8 ng of Cr, 0.4 ng Mn, 100.4 ng of Fe.

Conclusion: At high temperature, inhalation of transition metals present in cannabis could reinforce the deleterious effects of tar in smokers. For the purpose of commercialization and/or medicine manufacture, soils should be controlled and alternatives to the burning of cannabis should be encouraged.

P-02

Cannabidiol Effects Viability of Breast Cancer Cell Lines that Express CB1 and CB2 Receptors

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Background: The vast majority of all known breast cancers are estrogen receptor (ER) positive. Current treatment includes tamoxifen, which binds to ER and inhibits estrogen dependent transcription. Apart from that, (endo) cannabinoids have recently been demonstrated to affect progression and induce anti-tumor responses in certain cancer types, including breast cancer. Endocannabinoid receptors (CBs) include G-proteins found in the central nervous system (Type 1 receptor, CB1) and in the immune system (Type 2 receptor, CB2). Recent studies have also shown that tamoxifen metabolites and isomers act as inverse agonists on CBs, and are toxic in an ER-independent mechanism.

Objectives: To evaluate expression of CB1 and CB2 receptors in breast cancer cell lines of different subtypes and with different hormone status (ER+/PR+/HER2–, ER–/PR–/HER2+ and triple-negative).

To measure the effect of pure CBD, alone or in combination with tamoxifen and chemotherapy on viability of breast cancer cell lines.

Methods: Breast cancer cell lines (MCF7, MDA-MB-231, MDA-MB-361, T-47D, SK-BR-3) were cultured using standard cell culturing protocol. The expression levels of CB1 and CB2 receptors in breast cancer cell lines were analyzed using immunocytochemistry, comparing two different primary antibodies. We tested one of the commercially most used polyclonal antibodies against CB1 and CB2 receptors (manufactured by Abcam), and were among the first to test the new monoclonal antibody against both CBs (manufactured by Santa Cruz Biotechnology). The effect of pure CBD, tamoxifen and chemotherapy was measured using MTT assay.

Results: CB1 and CB2 receptor expression results differ among the cell lines and the used antibodies and also show the unspecificity of Santa Cruz antibodies. Breast cancer cell lines that express CB1 and CB2 receptors have reduced viability after the treatment with pure CBD, including the aggressive triple negative line.

Conclusion: The results propose CBD as a useful treatment for different breast cancer subtypes.

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P-03

Cannabinoids Affect Viability of Differentiated Glioblastoma Cells and Stem Cells Derived from Patients with Different CB1 and CB2 Receptor Levels

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Background: Glioblastoma (GB) is the most aggressive and therapeutically non-responsive primary brain tumour. Survival of patients ranges from 12 to 15 months after the diagnosis, in spite of improved treatments in irradiation and chemotherapy. This is mainly due to inefficient targeting of therapeutically resistant glioblastoma stem cells (GSCs), therefore new adjuvant treatment options against GSCs are urgently needed. Increasing number of preclinical studies have shown that cannabinoids induce the processes leading to anti-tumour responses in some types of cancer, including glioblastoma.

Objectives: To evaluate expression of CB1 and CB2 receptors in a small cohort of GB patients, in patient-derived tumour tissues, primary cultures of GB cells, GSCs and in established GB cell lines. Secondly, to identify most effective cannabinoids, their ratios and combinations with chemotherapeutic (Temozolomide-TMZ) to alter GB and GSC cell viability/cytotoxicity, apoptosis and proliferation.

Methods: Primary GB and GSC cell lines were established from a set of patient GB tumours. We analysed the expression profile of CB1 and CB2 receptor on GB tissue sections, patient derived glioblastoma cells and GSCs by immunolabelling. The effect of cannabinoids on GB cell viability, apoptosis and proliferation was studied using MTT assay, AnnexinV FC and Ki67 immunostaining.

Results and Conclusions: CB2 receptor was highly expressed in all tumour tissue samples while differentiated GB cells express moderate level of both receptors, in contrast to high levels of CB1 and CB2 in GSCs. Cannabinoids, especially at higher THC concentrations reduce viability of GB cells. The response to cannabinoids was even higher on GSCs. No synergistic effects between cannabinoids and TMZ under our experimental conditions was observed. These conditions did not reduce GB proliferation nor induce apoptosis.

We conclude that targeting GSC with cannabinoids may turn out to be promising adjuvant strategy to reduce glioblastoma growth.

P-04

Oxidative Stress Responses and Cholinesterase Activity in Blood and Brain of Wistar Rats Exposed to Δ^9-Tetrahydrocannabinol

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Background: Today, we are faced with the increasing use of illegal highly concentrated Δ^9-tetrahydrocannabinol (THC) preparations as supportive therapies for various malignancies and neurological disorders. Due to the fact that some, such as cannabis oils and butane hash oil, may contain over 80% of THC, their consumers can become intoxicated or experience various detrimental effects.

Objective: The aim of this study was to assess the toxic effects of THC in male Wistar rats orally exposed to 7 mg/kg b.w. THC, which is comparable to the dose find in illicit preparations.

Methods: The rats were sacrificed 24 h after treatment and plasma and brain samples were collected and stored for biochemical analyses. We determined the extent of oxidative stress as well as changes in activities of plasma and brain cholinesterases (ChE) in THC-treated and control rats.

Results: Acute oral administration of 7 mg/kg b.w. THC did not cause changes in oxidative stress biomarkers in rat plasma, but did cause a significant elevation of TBARS and GSH concentration and a drop in SOD activity was observed in brain tissue. Cholinesterase activities were not affected either in the plasma or in brain tissue.

Conclusion: The present study contributes to existing knowledge with evidence that acute exposure to a high THC dose induced oxidative stress in the brain, but did not affect changes in ChE activity.

P-05

Effect of Irinotecan on Urinary Δ^9-Tetrahydrocannabinol Elimination in Wistar Rats

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Background: Due to growing public interest in the antitumor potential of Δ^9-tetrahydrocannabinol (THC) and its possible role as an agent for alleviating side-effects of chemotherapy with irino-

tecan (IRI), some oncology patients have begun to reach for highly concentrated THC preparations. Since IRI, THC and their metabolites are subjected to glucuronic acid conjugation via the same enzyme (UGT1A1), co-administered THC could reduce IRI metabolism and clearance of its metabolites (particularly SN-38), leading to enhanced toxicity.

Objective: The aim of the study was to compare the urinary elimination of free (non-conjugated) THC and its metabolites [11-hydroxy-Δ^9-THC (THC-OH) and 11-nor-9-carboxy-Δ^9-THC (THC-COOH)] in IRI+THC treated rats with rats treated only with THC.

Methods: Male Wistar rats (N = 5 per group) were administered a combination of a single dose of IRI (100 mg/kg b.w, *i.p.*) and THC (7 mg/kg b.w., *p.o.*) or THC only. Urine samples were collected during the first 24 h after the treatment. THC, THC-OH and THC-COOH concentrations were determined by gas chromatography-mass spectrometry.

Results: Enhanced urinary THC-OH and THC-COOH excretion was noted in rats administered combined treatment compared to single THC treatment.

Conclusion: Increased non-conjugated THC metabolite urinary concentrations in combined treatment might point to the competition of THC and IRI for the same enzyme in phase II metabolism. Further studies are needed to elucidate the increase of the free fraction of THC metabolites in the concomitant use of IRI and THC.

P-06

Effects of Δ^9-THC and Cannabidiol on the Startle Response and Pre-Pulse Inhibition in A2a$^{-/-}$ Mice, a Murine Model of Schizophrenia.

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Background: Schizophrenia is a multifactorial disease characterized by alterations in dopaminergic, glutamatergic, and adenosine neurotransmission in limbic and cortical areas of the brain. Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the two most prominent active molecules in cannabis. In humans, acute activation of central type-1 cannabinoid receptors (CB1R) by THC can precipitate first-episode psychosis and chronic consumption may increase vulnerability to schizophrenia. On the contrary, CBD seems to attenuate unwanted psychological side effects of THC, such as paranoia, anxiety or psychosis, and has been investigated as a clinical candidate for schizophrenia.

Objective and Methods: We investigated the effects of THC and CBD on mice lacking adenosine receptors A2a, a murine model of schizophrenia. Male wild-type (WT) and knock-out (KO) mice were injected with THC (5 mg/kg), CBD (1 and 10 mg/kg) or a combination of both, and then tested for their startle response to an aversive auditive stimulus. The inhibition of such response by the presentation of a weaker auditive clue (pre-pulse) was also measured.

Results: THC increased the startle response in KO but not in WT mice, an effect that was normalized by the co-administration of CBD. CBD did not modify the startle response when given alone. However, the lower dose of CBD reduced the pre-pulse inhibition in WT animals but not in KO mice. Contrary to what expected, THC had no influence on this psychotic phenotype. Interestingly, combination of THC with the lower dose of CBD displayed the highest pre-pulse inhibition in both genotypes.

Conclusion: Our results indicate that THC may increase the sensitivity to aversive auditive stimuli in A2a KO mice selectively, an effect that is reversed by CBD co-administration. Our pre-pulse inhibition data contrast with the literature and point towards a combination of THC and CBD as the most effective treatment to reduce this psychotic phenotype.

P-07

Development of Standard Operating Procedures for the Preparation of *Cannabis*-Based Capsules

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Background: *Cannabis* for medicinal purposes may be administered, according to the Italian law, orally in the form of decoction or oil extract. The inhaler route is also allowed. Water-based extraction methods (decoction) do not allow the recovery of a high quantity of cannabinoids. On the other hand, the oil has a good extractive efficiency, but the bad organoleptic features may reduce the adherence to treatment.

Medical *Cannabis* available right now in Italy are the Dutch varieties, the Canadian and the Italian ones (FM1 and FM2).

Objective: The aim of the study was to facilitate the intake of *Cannabis* by developing an appropriate pharmaceutical form.

Methods: FM2 flowering tops, olive oil, capsules and a suitable excipient were used to develop a specific encapsulation method.

Content analysis of THC and CBD was performed using a fast ultra-high performance liquid chromatography tandem mass spectrometry (UHPLC-MS/MS) assay.

Results: We developed standard operating procedures for the preparation of capsules containing *Cannabis* oil extract and an appropriate excipient in order to jellify or adsorb the oil. Oil extract was prepared in a water bath with preheated FM2 flowering tops and olive oil (the specific procedure for *Cannabis* oil production is under patent application). The oil was included in capsules in quantities that meet the usual MD requests of THC and CBD. The content analysis confirms a homogeneity in the cannabinoids quantity between capsules (±10% – satisfying Pharmacopoeia assays –).

We also assessed that this pharmaceutical form does not interfere with the stability of the cannabinoids present in the oil.

Conclusion: These capsules may be an excellent way of administration for all kinds of patients but especially for those that may have difficulty swallowing large quantities of liquids.

P-08

Preliminary Studies on Cytotoxic Effects of Medical *Cannabis*-Based Preparations on MCF-7 and ARPE-19 Cell Lines

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Background: The availability of numerous varieties of medical *Cannabis* usually containing more than 500 active molecules in varying proportions, entails the need to carry out a correct evaluation about how different phytocomplexes may affect cytotoxicity.

Methods: Cytotoxicity of oil and ethanolic extracts was at first tested on MCF-7 cell line. The samples were prepared with *Cannabis* FM2 (5–8% THC; 7–12% CBD) and were characterised by different ratios of THC and CBD obtained properly changing extraction methods. Moreover the same samples of oil extract and some ethanolic solutions of pure THC and CBD were tested on ARPE-19 cell line. Cell growth inhibition was evaluated by sulforhodamine B colorimetric proliferation assay modified by Vichai and Kirtikara. Samples have been incubated for 24, 48 and 72 hours.

Results: Every sample turned out to be toxic when concentrations are greater than 10 μg/ml. For lower concentrations, the greatest toxicity of oil extracts has been detected at 24 hours on both cell lines. Whereas, at 48 and 72 hours, a cell regrowth has been observed. Ethanolic extracts showed the same behavior on MCF-7 cells, in particular those samples with ratios of THC and CBD similar to oil ones. Some ethanolic solutions of pure THC and CBD showed a growing cell viability after 24 hours. This increase has been detected in a greater way in the blend containing THC and CBD in the same ratio of the oil extract even if this solution in general showed to be the most toxic.

Conclusions: Our results suggest that specific THC and CBD ratios may give greater toxicity on cells than others, so further studies are needed also to understand why and which experimental conditions promoted the cell regrowth.

P-09

Medicinal Cannabis in Gilles de La Tourette Syndrome and Obsessive Compulsive Disorder with an Improvement of 12 Points on the Yale Global Tic Severity Scale: Case Report

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We report the case of a 32-year-old man, born in Barcelona. He was diagnosed with GTS at the age of 6, and later with obsessive-compulsive disorder OCD. In relation to GTS, he presents simple and complex motor tics: facial grimacing, shoulder shrugging, head and shoulder jerking, extensions of the arms, jumping and twisting. Regarding the phonic tics he presents simple and complex ones: shouting, sneezing, snorting, grunting, echolalia, coprolalia. This set of tics has changed over time when it comes to intensity and frequency. All this has generated emotional and social adaptation issues.

He received different pharmacological treatments for many years (risperidona, haloperidol, pimozida) with little improvement of the symptoms, in addition to many side effects which led him to abandon all the prescribed drugs at age 17. In December 2018, he came to us for a clinical assessment and he started treatment with MC at low doses of CBD/THC oil (5%/5%) sublingual which was gradually increased through medical monitoring until reaching the desired effect. After a four months treatment, we achieved an improvement of 12 points in the YGTSS and we introduced vaporization of CBD 15% on demand in moments of greater anxiety and exacerbation of the symptoms. We still have no conclusive results regarding this last intervention. Currently he is taking 2-1-3 drops of THC/CBD 5%/5% (1000 mg/10 ml).

In the first days of treatment with MC, the patient reported few side effects including spontaneous giggles, palpitations, slight drowsiness, euphoria, which all disappeared within a few days of treatment.

After four months of treatment with MC there has been an improvement of the symptoms as measured through the YGTSS. In addition, the patient refers a significant improvement of his quality of life and well being.

P-10

Effects of High Cannabidiol, Whole Flower Extract on Total Hemoglobin Variability and Pressure Alleviation during Squat-Stands Post-Concussion: Case Study

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Background: Cannabis sativa contains neuroprotective phytocannabinoids (cannabidiol, CBD; tetrahydrocannabinol, THC) which can interact with the body's endocannabinoid system. Administration of CBD and THC in combination with the other terpenoids in the plant allow for an entourage effect in which the therapeutic properties of each compound are elevated.

Objective: The purpose of this case study was to observe changes in total hemoglobin (tHb) variability and mean arterial pressure in a subject self-administering escalating dosages of a whole flower cannabis sativa extract (50:1 CBD:THC with whole flower profile; 100 mg CBD per mL).

Methods: The participant was attached to a blood pressure cuff using finger plethysmography for blood pressure metrics, and near infrared spectroscopy to monitor right prefrontal cortex for cerebral hemodynamic activity. Following 5 minutes of rest, the participant stood for 1 minute and was guided through a baroreflex squat stand maneuver (10 s squat, 10 s stand; 0.05 Hz) for 5 minutes to asses for cerebral autoregulatory changes. The participant

repeated this protocol at baseline (BL; no extract), week 2 (100 mg CBD/day), week 4 (200 mg CBD/day) and week 8 (400 mg CBD/day).

Results: The change in mean arterial pressure (first 6 s – last 4 s of squat) increased from 11.3 mm Hg at BL to 16.6 mm Hg at week 8 (47% increase). tHb standard deviation during squat stands increased from 0.74 μM at BL to 1.47 μM (99% increase) at week 8.

Conclusion: These preliminary results provide insight to the physiological changes of an escalating dose of whole flower cannabis extract.

P-11

No Abstract Allocated

P-12

Metered-Dose Cannabis Inhaler Provides Consistent, Dose-Related THC Blood Concentration and Analgesic Effects, in Patients with Chronic Neuropathic Pain

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Background: Currently, medical cannabis treatments' dosing is imprecise. Consequently, balancing between symptom relief and adverse events remains challenging. Therefore, administration by smoking or vaporization as standard treatment is limited, and physicians are reluctant to prescribe medical cannabis. Syqe Medical developed a thermal-metered-dose cannabis inhaler delivering low, precise and selective therapeutic doses of Δ^9-THC from raw cannabis.

This study tested the pharmacokinetic profile, safety, and analgesic effect of a single inhalation compared to placebo, in adult patients suffering from chronic pain.

Methods: In a randomized, 3-arms, double-blind, cross-over, placebo-controlled clinical trial, 27 patients were enrolled to receive, in three study sessions, a single inhalation of Δ^9-THC: 0.5 mg, 1 mg or placebo. THC pharmacokinetic profile, pain intensity, safety parameters and cognitive tests were performed at pre-defined time points in each session.

Results: Following inhalation of 0.5 mg or 1 mg, Δ^9-THC plasma Cmax±SD was 14.3 ± 7.7 ng/ml and 33.8 ± 25.7 ng/ml respectively. Tmax ± SD was 3.7 ± 1.4 and 4.4 ± 2.1 minutes respectively. $AUC_{0\rightarrow infinity}$ ± SD was 300 ± 144 ng*min/ml and 769 ± 331 ng*min/ml, respectively.

Both 0.5 mg and 1 mg doses showed a significant reduction in pain intensity compared with baseline (maximum change in VAS score was 24.97% and 39.42% respectively. *P0.0001*), that remained stable for 150 minutes. Furthermore, the 1 mg dosage showed significant pain decrease compared to placebo (*P0.0001*). Adverse events were mild and resolved spontaneously. There was no evidence of consistent impairment in cognitive performance.

Conclusions: Syqe inhaler demonstrated effective delivery of low, precise and selective therapeutic doses of THC, enabling individualization of medical cannabis regimens that can be evaluated pharmacokinetically and pharmacodynamically using accepted pharmaceutical models.

P-13

Occurrence of Brief Psychotic Disorder (BPD) in the Cannabis Consumers: Study of THC and CBD Concentrations in Hair

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Background: Among young consumers of cannabis, a BPD can be either the clinical manifestation of an Acute Cannabis Psychosis (ACP) or an announcing event of schizophrenia's onset.

Objective: To discriminate ACP from non-affective psychotic disorders (NAPD) (delusional disorder and schizophrenia).

Method: We measured THC and CBD concentrations in hair among four different groups of New Caledonian patients, all cannabis consumers (N = 243).

Group 1: 61 patients hospitalized for medical or surgical reasons (Control).

Group 2: 88 patients undergoing psychiatric follow-up for the treatment of NAPD.

Group 3: 30 patients undergoing psychiatric follow-up for the treatment of ACP.

Group 4: 64 patients with other psychiatric disorders (OPD) (borderline personality disorder, mood disorder...).

After sampling a 3 cm proximal length of head hair, THC and CBD were assayed by GC-MS (LOQ: 0.05 ng/mg). Results were statistically analyzed by the nonparametric Kruskal-Wallis test.

Results: There is a significant difference between the three groups of patients with psychiatric disorders. This difference is more marked between NAPD patients and ACP patients. In addition, after logarithmic transformation, data show that control subjects have a significantly higher CBD/THC ratio than patients in other groups.

Conclusion: This study shows that, considering capillary THC concentrations and CBD/THC ratio, it can be possible to discriminate NAPD from ACP patients among cannabis users who exhibit a BPD. Moreover, it can help predicting people with schizophrenic risk. Besides, this study emphasizes the protective role of CBD in the appearance of any acute or chronic psychosis.

P-14

In Utero Exposure to Uncontrolled Cannabis in New Caledonia

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Background: During pregnancy, THC freely passes the blood-placental barrier and its concentration in the fetal blood is at least equal to that of the mother. Regarding the immediate impact of cannabis consumption during pregnancy, the risks mentioned could be: intrauterine growth retardation, intrauterine fetal death, decreased uteroplacental perfusion, etc.

Objective: To assess the prevalence of pregnant women who use cannabis in New Caledonia; as well as the possible consequences for the child, due to cannabis use during pregnancy.

Methods: From 2014 to 2017, 3072 sera of pregnant women were tested. In parallel, 13 files of children exposed in utero to cannabis were selected

Results: 142 sera (4.6 %) were positive for THC and/or one of its metabolites. However, there was a difference between the first pregnancy trimester (more than 6 % positive) and the second trimester (2 % positive). Of the 20 known pregnancy outcomes of consuming mothers, 4 were pathological (2 oligoamnios, 1 plagiocephaly, 1 intrauterine fetal death). Among 13 children tested positive at birth and/or whose mother reported using cannabis, 9 had neurological and/or morphological abnormalities at birth. Moreover, at 10 years old – regarding the late impact of cannabis consumption during pregnancy – children may present attention deficit hyperactivity disorder or impulsivity.

Conclusion: Although it is difficult to apprehend the role of possible co-consumptions of alcohol and tobacco in these disorders occurrence, it should be possible, according to this study, to identify consumers and their children exposed in utero; these children could benefit from careful monitoring from childhood to the end of adolescence.

P-15

How Patients Decide What Medical Cannabis Products to Use for Chronic Pain: The Patient-Dispensary-Doctor Interface

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Background: Currently, over 68,000 patients are enrolled in the New Mexico (USA) Medical Cannabis Program. The top three of 22 qualifying conditions are Post-Traumatic Stress Disorder, Chronic Pain and Cancer. Available products tend to differ depending on which specific strains are grown and formulations manufactured by each producer. Rigorous research on the effectiveness of available products is lacking. As a result, evidence-based information is lacking on what doses or formulations are effective for specific medical conditions. Therefore, new medical cannabis (MedCan) patients do not know how to make decisions on which available products will be effective for their symptoms.

Objective: To define how MedCan patients make decisions about what products, formulations, and doses to use for chronic pain.

Methods: Rigorous qualitative study: a) interviewed MedCan patients, dispensary sales associates/management and primary care doctors; b) analyzed patient decision-making processes on MedCan treatment.

Results: Primary care doctors do not know how to counsel their patients on what MedCan products are effective. MedCan patients consult dispensary staff who use anecdotal evidence or popular websites instead of systematic research to advise patients. Patients use multiple products simultaneously in an iterative process and experiment until they decide what products and dosages work best. They eventually narrow their use to specific products to treat specific symptoms, such as pain, anxiety or insomnia. Many chronic pain patients decrease their opioid use by substituting MedCan to treat their pain.

Conclusion: Despite the fact that MedCan products vary significantly by producer, there is a need to conduct rigorous research on what available products, dosages and chemical contents are most effective for chronic pain and other medical conditions. The results could inform patient educational programs, physician continuing education, and MedCan dispensary staff education.

P-16

Retrospective Review Evaluating Symptom Outcomes in Patients with Multiple Sclerosis Using KANOBIL® MS as Adjunctive Symptomatic Treatment

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Background: Multiple Sclerosis (MS) affects more than 2.3 million people worldwide. In R. of N. Macedonia approximately 2000 people are affected, out of whom 1250 have been registered as patients at University Clinic of Neurology (UCN) in Skopje.

Cannabis-based treatments for MS have been one of the most scientifically researched with recommendations for its use for additional treatment of certain symptoms of MS.

Objective: The purpose of this retrospective review is to evaluate symptom outcomes in patients with MS who have utilized KANOBIL® MS as adjunctive symptomatic treatment for improving spasticity.

Methods: This Retrospective review evaluated outcomes of use of KANOBIL® MS, oil solution, containing 2 mg THC and 1 mg CBD/1 ml, as additional treatment for spasticity in 30 MS ambulatory patients from UCN.

Evaluation was performed by following: 1. efficacy of treatment as primary measured by change in spasticity, dose-dependant response and secondary measured by pain, sleep difficulty, motricity and quality of life response; 2. tolerability as measured by frequency of appearance, strength of adverse events and withdrawals due to lack of efficacy. Efficacy and tolerability were assessed by review of patient medical history records and patient examination using various scales for period before treatment (baseline), at Week 4 and at Week 8/12 of treatment.

Results: The data from patient medical history records will be tabulated and presented with analysis on improvements on studied outcomes and adverse events. Patient reported outcomes and adverse events as well as withdrawals, will be tabulated, compared to baseline and statistical analysis will be performed and presented.

Conclusion: The use of medical cannabis for symptom management for patients diagnosed with MS is becoming more widely accepted. This review, although retrospective, demonstrates patient reported benefits that are promising and further prospective trials with larger group of patients are warranted.

Limitation to the Review: Retrospective analysis, subjective response, results reported as perceived by patients, heterogeneous group of patients, adherence and length of treatment.

P-17

Practical Experiences and Perceptions of the Effects of KANOBIL® EPI as an Additional Treatment in Refractory Epilepsy in Children

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Background: Epilepsy occurs in 1–2% of the pediatric population, up to 40% of these children will not be seizure free while on antiepileptic drugs (AEDs). Cannabis-based treatments for epilepsy have generated much interest, and use of cannabis based products in the treatment of epilepsy is widely scientifically researched.

Objective: To describe the experiences of the effects of KANOBIL® EPI as additional treatment in refractory epilepsy in 20 children.

Method: A prospective observation describing the effect of KANOBIL® EPI, oil solution containing 15 mg CBD and 1 mg THC/ 1 ml, used as additional treatment for period of six weeks in 20 outpatient children with intractable epilepsy, resistant to 2 antiepileptic drugs.

Observation followed: efficacy of the treatment as measured by number and frequency of seizures and tolerability as measured by frequency and strength of adverse events. Efficacy and tolerability were assessed by parental diary report.

Results: Effects of treatment with KANOBIL® EPI were assessed in 17 children, due to lack of feedback information from parental diary. Treatment with KANOBIL® EPI, generally, yielded positive effect on seizure load. One patient was seizure free. Reduction in seizure frequency ranging (50–80%) was reported for five (~29%) patients, intermittent reduction of seizure frequency was reported for three children (~18%) and for three children (~18%) insignificant change in seizure frequency was reported. Five (~29%) patients withdraw the treatment: two due to no adherence to treatment, one due to operation procedure and in two patient aggravations of seizures were reported.

For 12 patients with different range of seizure reduction, all parents reported improvement in behavior and alertness, communication and mood, appetite and sleep.

No adverse reactions were reported.

Conclusion: The results of this observation are promising and further prospective trials with larger and more homogenous group of patients are warranted.

Limitation to the observation: small group of patient, heterogeneous basic diagnosis and symptoms, adherence to treatment, results reported as perceived by parents, length of treatment.

P-18

Medical Use of Cannabis in the Cordillera (Philippines)

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Background: Possession and use of cannabis in any form is illegal in the Philippines, and therefore research on cannabis is nil. There is current move in the Philippines congress to use of medical cannabis. Cordillera is a region in northern Philippines where land is popularly known to be highly suitable for growth of cannabis.

Objective: This qualitative study documented practices in the Cordillera on the production, processing and use of medical cannabis.

Methods: In this case series design, we conducted in-depth interviews, focused group discussion and participant observation of key informants. Snowball sampling was used until data saturation. The study was approved by the St. Cabrini Medical Center-Asian Eye Institute Ethics Review Committee.

Results (Preliminary): 10 key informants participated after assurance of full anonymity. Cannabis is not indigenous to the Cordillera but brought by foreigners half a decade ago. The species that grows there is *Cannabis sativa* but hybrids may have emerged. Medical cannabis is traded as fresh or dried leaves, buds and seeds, and oil and used orally as tea or oil drops on drinks. Participants attested to medical benefits in pain (dysmenorrhea, toothache, arthritis, muscle and bone aches, wound pain), easing anxiety and depression, improving sleep, enhancing appetite and bowel movement, improving virility and fertility, and for general health to strengthen the immune system. Topical ground fresh leaves heal wounds, bites and skin allergies. Medical cannabis is usually prepared by women as home remedy. Excess use is associated with sleepiness and dry mouth. There was no addiction reported in medical use.

Conclusion: Medical cannabis has been used for decades in the Cordillera. Health benefits are documented in pain, sleep disturbance, and mental health. Addiction was not reported. This preliminary result will spur *basic* and *clinical* research to support safe and judicious use of medical cannabis in the Philippines.

P-19

Cannabis Medicines – Absolutely Safe?

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Background: NSW Cannabis Medicines Advisory Service (CMAS) is a State government funded advisory service providing clinical guidance to doctors considering prescribing a cannabis medicine (CM). To our knowledge, this service is the first of its kind in the world. It is widely assumed by the community that cannabis medicines are absolutely safe and not associated with patient morbidity and deaths. However, there is increasing concern that this assumption is incorrect and unsafe [1–7]. Locally, reports of CM adverse effects to NSW CMAS, NSW Poisons Information Centre (PIC) and local hospitalisations [8] have highlighted the need for greater pharmacovigilance for cannabis based medicines.

Objective: To evaluate the use of a pilot pharmacovigilance model developed by the cannabis medicine adverse effect reporting pathway working group (CMARP) to capture data about CM adverse effects. The project will also provide educational resources and knowledge to clinicians about CM adverse effects and reporting pathways, in collaboration with the Australian Centre for Cannabinoid Research and Excellence (ACRE).

Methods: Following stakeholder consultation, the pilot pharmacovigilance model will be released into the public domain. Educational resources will be used alongside the pilot data to highlight the adverse effect reporting pathway and widely disseminate information about previously under-reported CM adverse effects. Adverse effect data collected pre and post-intervention will be analysed to determine whether implementing these interventions facilitates adverse effect reporting.

Conclusion: The CMARP collaboration will develop a pilot pharmacovigilance model for cannabis medicines, designed to capture previously under-reported adverse effects. CM adverse effect educational resources for clinicians will also inform safer use of cannabis medicines.

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P-20

Illegal Cannabis Use is Common among Danes with Multiple Sclerosis

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Background: Use of cannabis to alleviate multiple sclerosis (MS)-related symptoms is increasing. Due to strict regulations, only a minority of MS patients receive cannabis-based prescription drugs. The extent of recreational and medical cannabis use among Danes with MS is unknown.

Objective: Our aim was to evaluate the prevalence of illegal and legal use of cannabis in MS patients, as well as reasons for use and perceived adverse effects.

Methods: An anonymous questionnaire was sent to all 3606 patients at the Danish Multiple Sclerosis Center, Rigshospitalet, University of Copenhagen. The questionnaire included questions about sociodemographic factors, clinical characteristics and medical or recreational cannabis use.

Results: Questionnaires were completed by 2244/3606 (62%), of which 2009 questionnaires from patients with MS or clinical isolated syndrome (CIS) were valid for analysis. Forty-nine percent (980/2009) had used cannabis at least once. Cannabis was used within the past year (current user) by 21%, and only 21% of those received prescribed cannabis-based medicine. Recreational use was reported by 17%. The primary reasons for use were to alleviate pain (61%), spasticity (52%) and sleep disturbances (46%). The most common adverse effects were drowsiness (30%), feeling quiet/subdued (23%) and dizziness (13%). Almost half (44%) of the non-cannabis users would consider use of cannabis to alleviate MS symptoms if the drug was legalized.

Conclusion: This study shows that illegal cannabis use is common among Danes with MS as only 21% of the current cannabis users received prescribed cannabis-based medicine. Current cannabis users reported high efficacy in relieving pain, spasticity and sleep disturbances. In addition, only mild to moderate severity of adverse effects were reported. To the best of our knowledge, this is the most comprehensive survey of cannabis use among MS patients.

P-21

Replacement of BEnzodiAcepines by Cannabinoids for tHe Preoperative Medication – A Feasibility Trial (BEACH-Trial)

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Objectives: BEACH is a feasibility study conducted to find out whether it is practicable to admit cannabidiol orally 1 hour preoperatively to substitute the routine premedication with benzodiazepines. This patient-oriented research study examines the effects of cannabidiol as a substitute for midazolam considering its possibilities of mental sedation. At present, the premedication with benzodiazepines in elderly patients is subject to controversial discussions among anesthesiologists as benzodiazepines given as anxiolytic medication before an operation to enhance the satisfaction of the patient with the overal in-hospital experience can cause negative side effects.

Interventions: Cannabidiol will be admitted to the patient one hour pre-operatively in two different doses (150 mg and 300 mg). The blood level of Cannabidiol will be tested preoperatively in 20 min steps to evaluate the most effective time for administration. We plan to include patients who undergo elective surgery with a minimum duration of 30 minutes under planned general or combined regional and general anaesthesia will be included. Excluded will be patients under chronic benzdiazepine or cannabinoid treatment or patients with contraindications for benzodiazepine or cannabinoid application. Patients with severe psychiatric disorder or a expected continuous mandatory ventilation after surgery will also be excluded.

Outcome: We are planning to measure and record the effects on the patient's outcome regarding overall satisfaction with the perioperative process (e.g. preoperative anxiety, patient cooperation, well-being, pain and sleeping), postoperative nausea or vomiting, nosocomial infections, the occurrence of inflammation and POD and as a consequence the quality of living 30 days after the hospital stay. Other secondary outcome parameters will be the functional and cognitive recovery, the time from end of anaesthesia to extubation, length of stay in the hospital and if applicable the Intensive-Care-Unit.

Outlook: If the results of the feasibility trial are promising a major randomized controlled trial is planned to confirm the findings.

P-22

The Effect of Medical Cannabis on Neuropathic Pain and Spasticity in Patients with Multiple Sclerosis and Spinal Cord Injury: A Danish Multicentre Double-Blinded Placebo-Controlled Study

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Background: Disease or acquired damage to the central nervous system may lead to invalidating spasticity and central neuropathic pain (NP). Multiple sclerosis (MS) and spinal cord injury (SCI) are two diseases where these symptoms are frequent and prominent. Patients with MS and SCI often possess a great desire for being treated with cannabis-based medicines (CBM). In Denmark it is politically determined that doctors can prescribe CBM in a four-year trail basis. Little is known about effect, side-effect and doses of CBM

Objective: To examine if CBM is a relevant and safe treatment for spasticity and NP for patients with MS or SCI.

Methods: In a national multicentre study, we examine the effect of CBM on NP and spasticity in a double blinded design. Patients will be randomized for treatment with either THC, CBD, combination THC&CBD or placebo. 448 patients will be included, and duration of treatment is seven weeks. Primary endpoints are patient reported pain and spasticity. Secondary endpoints include quality of life and sleep. Registration of depression and anxiety. Relief of pain and spasticity and a range of clinical tests. Further, we describe the adverse event profile of cannabinoids

In a sub-study of 40 patients we examine pharmacodynamics and pharmacokinetics of CBM to gain more knowledge about blood concentration, duration of effect and drug excretion.

Discussion: There is a need of knowledge regarding use of CBM for the treatment of NP and/or spasticity. The description of the adverse reaction profile is important in determining whether treatment may be recommended in the future.

P-23

The Current State of Cannabinoids for Medical Use in South Korea

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The use of cannabis in Korea is illegal and is strongly regulated by law. The medical efficacy of cannabinoids has been internationally proven over the past decade, and it has also been developed as a drug in pharmaceutical companies. In Korea, the medical use of cannabinoids has been legalized since 2018 through continuous requests from patients suffering from refractory diseases and coordination between government departments. However, even now, the use of cannabis for recreational use is strictly prohibited. After the law was enacted in 2018, medical cannabinoids began to be used in March 2019. In Korea, medical cannabinoids can be supplied through the Korean Orphan & Essential Drug Center. The guardian must apply for hemp application and medical certificate directly to the Korea Food and Drug Administration (FDA). If the application is approved by the Korea FDA, the guardian can use medical cannabinoids. The use of cannabinoids for medical use in Korea is very limited and a nationwide prospective study on drug efficacy and safety is needed.

P-24

Medical Cannabis in the Treatment of PTSD – A Case Series

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Background: Posttraumatic stress disorder (PTSD) is an often chronic and debilitating condition, from which a significant number of patients does not fully recover. Only two medications (sertraline and paroxetine) are registered for its treatment and there hasn't been much progress in the development of new medications (Krystal et al., 2017). Recently there has been an increased interest in the endocannabinoid system as a pharmacological target for the treatment of PTSD, and several studies have reported promising results using cannabinoids in treating the symptoms of this disorder (Steenkamp et al., 2017; Passie et al., 2012). With a growing number of countries legalizing the medical use of cannabis, cannabinoids are increasingly being prescribed for patients with PTSD. However, results of randomized clinical trials into its safety and efficacy are still lacking, and there are many unknowns regarding optimal dosages and cannabinoid ratios (e.g. THC/CBD), routes of administration, and potential side effects.

Objective: To learn more about patients` experiences using medical cannabis for PTSD. Their preferred cannabis strains and routes of administration, dosages being used, specific symptoms being targeted, quality of sleep, efficacy compared to previously used medications, side effects, etc.

Methods: Six to eight patients with a prescription of medical cannabis for PTSD will be interviewed by phone, using a brief

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semi-structured interview. Additionally, all patients will be invited for a two-hour focus group discussion during which experiences will be shared and discussed. Data will be analysed both on a case by case basis and on a group level.

Results/Conclusion: This study is currently being conducted. Data gathering will be completed before the end of April.

P-25

Use and Safety of *Cannabis* for Medical Use in Italy

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Background: Since 2015 medical use of *Cannabis* is authorised and reimbursed in Italy within the National Health System for selected conditions. In 2016 the Military Pharmaceutical Chemical Works (Florence) was authorised for the production of *Cannabis* according to Good Manufacturing Practice.

Objective: To describe prescriptions of *Cannabis* and suspected adverse reactions (ARs) associated with *Cannabis* for medical use.

Methods: An hoc monitoring system was set up to collect prescriptions issued in Italy. Prescription web-based forms are filled in by physicians. Spontaneous reports of suspected ARs to natural health products (including galenic preparations containing herbals) are collected in Italy within the Italian Phytovigilance system coordinated by the National Institute of Health.

Results: At January 2019, 26,042 prescriptions, related to 12,998 patients, were registered. Mean age of patients was 58 years, women represented 63%. As for type of Cannabis, 2,438 prescriptions (9.4% of total) of the national product (FM2: 5–8% THC e 6–12% CBD) were collected. *Cannabis* was mainly prescribed for chronic pain; spasticity in multiple sclerosis and fibromyalgia. Dosage was very variable; i.e. a median daily dose of 114 mg (10°-90° percentile: 15–1000 mg) was prescribed for chronic pain. Almost in all prescriptions *Cannabis* was used as add-on to other therapies. At December 2018 103 suspected adverse reactions to *Cannabis* for medical use were reported. Median age of patients was 62 years (range 22–91), mainly women (76%). In 23 (22%) reports hospitalisation was indicated. The reactions reported were, mainly: psychiatric disorders, cardiovascular and allergic reactions, and lack of efficacy.

Conclusion: Our data allow to estimate the prevalence of medical use of *Cannabis* in the Italian population. *Cannabis* for medicinal use is usually well tolerated. The adverse effects collected were similar to that observed in clinical trials. It is important to continuously monitor safety *of Cannabis* medical use in the population.

P-26

Self-Reported Effectiveness and Safety of Trokie® lozenges: A Standardized Formulation for the Buccal Delivery of Cannabis Extracts

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Therapeutic use of cannabinoids, the main active ingredients of Cannabis sativa L., is often hindered by their limited bioavailability and undesirable psychoactivity. We conducted an observational study in December 2016 and another one in February 2018 to investigate respectively i) the effectiveness of Trokie® lozenges, a standardized formulation containing cannabis extracts, to deliver cannabinoids via buccal absorption and ii) its long-term safety. Participants were members of the Palliative Care Corporation health clinic, registered as cannabis users in the state of California, and had a diagnosis of chronic non-cancer pain. For the effectiveness study, 49 participants were asked to self-report pain perception before and after 1–12 weeks of taking Trokie® lozenges, using an 11-point pain intensity numeric rating scale (PI-NRS). A mean reduction in PI-NRS score of 4.9 ± 2.0 points was observed. Onset of analgesia typically varied between 5 and 40 minutes, which seems consistent with, at least partial, buccal absorption. In the safety study, 35 participants were asked to complete a questionnaire about adverse events (AEs) associated with Trokie® lozenges. AEs were reported by 16 subjects (46%), the most common being dizziness/unsteadiness (N = 7), bad taste (N = 5), and throat irritation/dry mouth (N = 4). None of the self-reported AEs resulted in a serious medical situation and most of them had limited impact on daily functions. Despite the AEs, 90% of participants reported being "satisfied" or "very satisfied" with the product. These observations suggest that buccal administration of standardized extracts via Trokie® lozenges may represent an efficacious and safe approach to cannabis administration.

P-27

Proposed Treatment of Refractory Epilepsy in Dogs

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Background: Epilepsy is the most common neurologic disease in small animals. The current treatment consists in the initial stage control the status epilepticus and the final goal is always the end of seizures. 70% to 80% of dogs tend to be controlled, the remaining 20% to 30% are the refractory epilepsy. Clinical trials in children and studies with animal models have been demonstrating the potentials of these new therapeutics, with special predominance to purified extracts of CBD or in combination with THC.

Objective: Some veterinarians are reluctant to use the product due to the lack of quality information concerns the safety of prod-

ucts, the administration route and therapeutic doses. A preliminary study of cannabis compounds has the objective of study the efficacy and safety of CBD/THC, in the treatment of refractory epilepsy.

Methods: A double blind clinical trial in 40 dogs, with refractory epileptic, of unknown or genetic aetiology. The initial dose of CBD/THC (5:1), will be escalated throughout the trial, with a duration of 9 weeks, until the improvement of the animal`s quality of life. The efficiency of treatment will be evaluated with a neurologic exam a survey to the owners concerning animal`s quality of life and EEG of 2 hours.

Conclusion: The main goal will be to provide high quality data of CBD/THC protocols in the treatment of refractory epileptic in dogs in relation to dosage and safety of active cannabinoids.

P-28

Cannabis Extracts Containing Terpenoids vs Synthetic Cannabinoids in Therapeutics

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Cannabis sativa L. (family Cannabaceae), a medicinal plant whose use record goes back more than two thousand years, contains in its composition more than one hundred phytocannabinoids, specially D^9-tetrahydrocannabinol (THC) and cannabidiol (CBD). However, this plant with a long history of use and purposes also has other biologically active components, namely cannabis terpenoids. Thus, the objective is to find evidence to understand the advantages and disadvantages in the use of extracts of this plant compared to the use of pure phytocompounds and their synthetic derivatives.

In conclusion, cannabis extracts, unlike pure compounds, presents several compounds that can act synergistically and can potentiate efficacy and reduce side effects and toxicity in humans.

P-29

Efficacy, Tolerability, and Safety of Cannabinoids for Chemotherapy-Induced Nausea and Vomiting

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There is growing public interest for the medical use of cannabinoids, for example, for chemotherapy-induced nausea and vomiting (CINV). A comprehensive literature search until November 2015 was conducted in MEDLINE, DARE and Cochrane libraries for systematic reviews of randomized controlled trials (RCTs) comparing herbal or pharmaceutical cannabinoids (CB) versus placebo or conventional antiemetics for CINV. Outcomes were reduction of CINV for efficacy, drop-out rates due to adverse events for tolerability, and serious adverse events for safety. The methodology quality of the systematic reviews was evaluated by the tool assessment of multiple systematic reviews (AMSTAR). Six systematic reviews of RCTs included the pharmaceutical CBs dronabinol, levonantradol, and nabilone or whole plant extract (e.g., nabiximol) compared with placebo or conventional antiemetics. There was moderate quality evidence on the efficacy of CBs compared to placebo and conventional antiemetics for CINV. There was moderate quality evidence that pharmaceutical CBs were less tolerated and less safe than placebo and conventional antiemetics in CINV. One RCT examining whole plant extract was included into the systematic reviews. No RCT was found comparing CBs with neurokinine−1 receptor antagonists. With safe and effective antiemetics available, CBs cannot be recommended as first- or second-line therapy for CINV. Some guidelines recommend pharmaceutical CBs as third-line treatment in the management of breakthrough nausea and vomiting. Due to the lack of RCT data and safety concerns, herbal cannabis cannot be recommended for CINV.

P-30

Register-Based Evaluation of Effects and Adverse Effects of Medicinal Cannabis in Denmark

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We are currently undertaking a three-stage evaluation of medicinal cannabis in Denmark, which was introduced experimentally in January 2018. This abstract deals with the largest of these parts of the evaluation. We are conducting a register-based evaluation of all people who have received medicinal cannabis since it was introduced in 2018, propensity-score matched to individuals with the same diseases who have not received medicinal cannabis. Both cases and controls will be identified through nationwide Danish registers. The registers will be linked using the unique Danish personal identification number. The following information will be assessed in these registers: Pain (identified as a range of medication prescribed); spasms (identified as a range of antispasmodics prescribed); nausea (identified also from medicinal products); infections (identified both through medicinal products and the National Patient Registry); gastrointestinal disorders (identified in those same two registers); overall use of medication; overall use of the secondary healthcare sector; overall use of the primary healthcare sector; intentional selfharm (identified through the National Patient Registry); occupational ability; cannabis-induced psychosis and other symptoms of cannabis use disorders (National Patient Registry and the Psychiatric Central Research Register); affective disorders and anxiety (same registers).

P-31

Interview and Survey-Based Evaluation of Effects and Adverse Effects of Medicinal Cannabis in Denmark

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We are currently undertaking a three-stage evaluation of medicinal cannabis in Denmark, which was introduced experimentally in January 2018. This abstract deals with two of these parts of the evaluation. We are conducting both a set of approximately 20 qualitative interviews which will be analyzed phenomenologically. Early impressions of these interviews will be presented at the conference. The second part of the evaluation deals with 200 quantitative clinical interviews and surveys conducted with two groups of individuals: 100 interviews with people who have received medicinal cannabis since 2018, and 100 propensity-matched controls who have not received medicinal cannabis. Both cases and controls will be identified through nationwide Danish registers. The following instruments will be used: Brief Pain Inventory, SF-36, WHO-DAS-II (disability assessment), WHOQOL-BREF (quality of life), Client Satisfaction Questionnaire, Pittsburgh Sleep Quality Index, the Hamilton scales for depression and anxiety, Peters Delusions Inventory, and the Repeatable Battery for the Assessment of Neuropsychological Status. Specific scales will also be used to assess chemotherapy-related nausea and MS-related spasticity, depending on the indications for which people have used medicinal cannabis.

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