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Since thousands of years, cannabis has been used as a fiber supplier, food, remedy, and intoxicant. The first written document on the medical use of cannabis originates from China. This basic work of medicine is attributed to the emperor Shen-Nung, one of the fathers of Chinese Medicine, who reigned around 2700 BC. From China, the plant seems to have spread to India around 800 BC, where it was rapidly valued as a medicine and recreative agent. Also, in Egypt the use of cannabis has been documented since around 1500 BC. The well-known *Papyrus Ebers*, for instance, provides several references to the medical application of cannabis at that time.

In Europe, interestingly, mainly the fibers and seeds of cannabis were used until the end of the 19th century; the herb as a remedy or intoxicant was almost unknown. The turning point was the year 1839, in which the Irish medical doctor William B. O’Shaughnessy, stationed in Calcutta (India), published a comprehensive study on the successful use of Indian hemp in the treatment of various ailments such as cholera, tetanus, convulsions, and rheumatism. The western school medicine reacted with great interest to these findings, as no adequate drug to treat these diseases was available at the time. Research on medical hemp was thus promoted, particularly in France, England, and Germany. Numerous scientific works and dissertations on medical cannabis were published in the following years. Around 1900, preparations containing cannabis – many of them manufactured by pharmaceutical companies – were widely used to treat pain, convulsions, insomnia, and asthma, amongst others.

While highly valued as a medicine around 1900, medical cannabis preparations almost completely disappeared in the middle of the 20th century. One major reason for this development was the medical-pharmaceutical progress at the time. Numerous new chemical compounds were discovered which replaced cannabis products in various medical applications, and vaccines were developed for the prevention of infectious diseases. Furthermore, hemp preparations lacked standardization, resulting in a controversy over their medical effect, and economic restrictions due to the two world wars impeded the import of Indian hemp to Europe. Finally, increasing legal restraints led to the worldwide prohibition of cannabis in 1961. In contrast to the recreative use of hemp, the medical significance of the plant almost fell into oblivion in the following years.

In the early 1990s, however, the situation began to change with the discovery of the endocannabinoid system and endogenous cannabinoid receptors (CB1, CB2) present in the human body. This revolutionary finding enabled the understanding of the thitherto more or less unknown mechanism of action of tetrahydrocannabinol (THC), the main active substance of cannabis. Since then, cannabis research experiences a veritable revival despite the still widespread worldwide ban on hemp. The future will show whether and in what forms cannabis will be reestablished in the daily practice of prescribing physicians and whether the high expectations can be corroborated by further studies.
Results obtained from preclinical pharmacological research, to which my laboratory has contributed, have recently revealed potential therapeutic uses for the following cannabinoids:

(1) Four phytocannabinoids. These plant cannabinoids are cannabidiol (CBD), cannabidiolic acid (CBDA), cannabigerol (CBG) and Δ⁸-tetrahydrocannabivarin (THCV). I will present preclinical evidence that suggests that (i) CBD, CBDA and THCV would ameliorate anxiety and chemotherapy-induced nausea and vomiting by enhancing the activation of 5-HT₁₅ receptors; (ii) CBG would relieve inflammatory pain by activating α₂-adrenoceptors; (iii) THCV would ameliorate diabetes-related kidney damage and nicotine dependence because it is a CB₂ receptor agonist but a CB₁ receptor antagonist (Pertwee, R.G., 2014, Handbook of Cannabis, Oxford University Press; Pertwee et al., 2018, Br. J. Pharmacol., 175: 100-112; Xi et al., 2019, Br. J. Pharmacol., in press).

(2) HU-580, a synthetic analogue of CBDA. The phytocannabinoid, CBDA, is more potent than CBD at enhancing 5-HT₁₅ receptor activation, and at reducing signs of anxiety and chemotherapy-induced nausea in animal models, but is not “druggable” as it is very unstable. However, its synthetic analogue, CBDA methyl ester (HU-580) produces these effects with even greater potency than CBDA, and is very stable, and hence might well be a highly effective medicine for the treatment of anxiety and/or chemotherapy-induced nausea (Pertwee et al., 2018, Br. J. Pharmacol., 175: 100-112).

(3) Synthetic positive allosteric modulators (PAMs) of cannabinoid CB₁ or CB₂ receptors. These are compounds that target allosteric sites present on cannabinoid CB₁ or CB₂ receptors in a manner that strengthens the direct (orthosteric) activation of one or other of these receptors by exogenously administered agonists and by endogenously released endocannabinoids. Turning first to synthetic CB₁ receptor PAMs, there is convincing preclinical evidence that GAT211 and GAT229 are CB₁ PAMs, and that by strengthening the endogenous activation of CB₁ receptors, (i) GAT211 reduces signs of inflammatory and neuropathic pain in mice without producing any signs of tolerance to this analgesia, or of dependence, (Slivicki et al., 2018, Biol. Psychiatry, 84: 722-733), and (ii) GAT229 reduces intraocular pressure in ocular hypertensive mice, and so may be effective against glaucoma (Cairns et al., 2017, J. Ocular Pharmacol. Ther., 33: 582-590). Moving on to synthetic CB₂ receptor PAMs, there is evidence that EC21a is one such compound, and that it might be anticarcinogenic since it can significantly enhance the ability of the selective CB₂ receptor agonist, JWH-133, to decrease markedly the viability of lymphocytic leukaemia blood cancer cells that highly express CB₂ receptors (Al Bakour et al., 2019, Br. J. Pharmacol., 176: 3057).

These findings increase the ever-growing need for research with human subjects directed at evaluating the clinical relevance of at least some of the many potential novel therapeutic uses of plant and synthetic cannabinoids that have been revealed by preclinical research.
EFFECTS OF THC, CBD AND CANNABIS: DIFFERENT OR ALL THE SAME?

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In several countries cannabis and cannabis-based medicine can be prescribed legally by medical doctors for the treatment of different conditions. In recent years, more and more different cannabis strains and cannabis-based medicines became available for medicinal use. For treating physicians, therefore, it is important to know about similarities and differences of these drugs. This is the more important, since prices may differ significantly and supply bottlenecks may occur.

Cannabis as the whole plant contains more than 115 different cannabinoids and, in addition, more than 500 other phytochemicals. Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the best studied cannabinoids, but several further cannabinoids have been identified such as cannabiol (CBN), cannabichromen (CBC), and cannabigerol (CBG). Among the phytochemicals particularly terpenes and flavonoids receive most attention. Preclinical studies provided substantial evidence for different beneficial effects of both chemicals including anti-inflammatory, anxiolytic, anti-cancer, and analgesic effects. However, until today cannabis strains are only standardized for contents of THC and CBD, but not of “minor” cannabinoids and phytochemicals such as terpenes and flavonoids. There is general agreement that psychotropic as well as several therapeutic effects of cannabis (such as anti-spasmodic, anti-vomiting, and analgesic effects) are related to THC. However, there is increasing evidence that terpenes and flavonoids work synergistically with the cannabinoids by influencing one another. For example, terpenes may influence the binding of THC to central cannabinoid CB1 receptors and interact with other neurotransmitter receptors. These synergistic interactions are termed as the “entourage effect.” However, until today it is unknown which composition of cannabinoids, terpenes, flavonoids, and other compounds provides best therapeutic effects.

Currently, in Germany, 26 different cannabis strains are available containing between 1-25% THC and <1-12% CBD. In addition, different cannabis full spectrum extracts can be prescribed for oral use standardized for THC and CBD (containing 5-25% THC and 1-10% CBD). Nabiximols is a cannabis extract standardized for THC and CBD in a 1:1 ratio. In addition, pure THC (=dronabinol) can be prescribed in different formulations. Its therapeutic effects include – among several others - anti-spasmodic, anti-vomiting, appetite increasing, and analgesic effects. Similar effects are attributed to nabimol - a synthetic cannabinoid structurally distinct from THC that mimics THC’s pharmacological activity. Finally, pure CBD is available as a non-narcotic prescription drug. CBD has anti-epileptic and presumably anxiolytic and anti-psychotic effects.

In Germany, only nabiximols (market as Sativex® for the treatment of spasticity due to Multiple Sclerosis) and nabimol (market as Canimes® for the treatment of chemotherapy-induced nausea and vomiting) were approved by BfArM. However, approval of the CBD extract Epidiolex® (for seizure reduction in patients with Lennox-Gastaut syndrome and Dravet syndrome) is expected soon.
CANNABIS: WHERE WE ARE AND WHERE WE’RE GOING

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This presentation will present a broad overview of the current state of cannabis research and therapeutics, examining the current status of its use in pain, nausea and vomiting, epilepsy, sleep disturbance, spasticity, dementia and cancer, as well as use in special populations. An assessment of current research challenges and roadblocks will also be discussed including funding, standardization, clinical trial design and placebo responses.

References:


Introduction: The first part of my talk will be an introduction to the endogenous cannabinoid system. In the second part I will present recent results from the lab as follows: Human use of cannabis is well known to stimulate the consumption of calorically dense, nutritionally poor food (AKA “the munchies”). Similarly, endogenous cannabinoids stimulate the consumption of highly palatable food in a number of preclinical studies. Thus, it is surprising that a substantial majority of epidemiological studies have found that chronic cannabis use is associated with reduced body weight, central obesity, risk for metabolic syndrome and type II diabetes, and inflammatory markers, despite a nutritionally poor diet. In an effort to understand the metabolically protective effects of cannabis, we have investigated THC’s interactions with GPR119, a nutrient-sensing G protein coupled receptor, found on pancreatic beta cells and gut enteroendocrine K and L cells and is activated by partially digested lipids. GPR119 activation is associated with increased insulin secretion and sensitivity, preservation of beta cell mass, and enhanced incretin secretion.

Methods: GPR119 signaling was assessed in HEK293 cells stably expressing GPR119 as well as GluTag cells endogenously expressing GPR119. Insulin secretion was assessed in MIN6 rat insulinoma cells. Wildtype C57BL/6J and GPR119 knockout mice were made obese by consuming a high fat diet (HFD; Research Diet D12331). These mice (both concurrent with initiation of HFD, or after obesity was established) were treated with vehicle or various drugs and their weights recorded.

Results: 1) THC and its metabolites activated GPR119 in a functionally-selective fashion, while CBD was ineffective, 2) THC and its metabolites inhibited secretion of GLP-1 from GluTag cells, but did not affect glucose-induced secretion of insulin from MIN6 cells, 3) THC, administered intraperitoneally or orally, induced reversible weight loss in wildtype, but not GPR119 knockout mice. 4) THC administered to adolescent mice, concurrently with a high fat diet, attenuated the weight gain induced by a high fat diet.

Conclusions: These results suggest that sustained use of cannabis might lead to weight loss (or attenuated weight gain) by activation of GPR119 by THC or its metabolites, increased incretin secretion and an overall improvement in metabolic health.

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INTERACTIONS AND SIDE EFFECTS

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Interactions can occur at the pharmacokinetic level and at the pharmacodynamic level. This can lead to mutual influence of drug levels as well as to strengthening or weakening of effector systems that are influenced by cannabinoids and other drugs.

Side effects may be acute, which may happen very often, while chronic side effects are rare and cannabinoids are usually well tolerated long-term, without significant unwanted effects on stomach, liver, kidneys and the heart.

**Pharmacokinetic interactions:** Both tetrahydrocannabinol (THC) and cannabidiol (CBD) are metabolized via the hepatic cytochrome P450 system (CYP450), including CYP3A4, CYP2C19 and CYP2D6. Interactions may result in increases of cannabinoid concentrations in the blood or those of other drugs metabolised by the same enzymes. This effect has been observed in antiepileptic medication, for example clobazam given conjointly with CBD. On the other hand, the simultaneous administration of the combination of THC/CBD with rifampicin, a strong inductor of CYP3A4 may lead to a significant reduction of the concentration time values of the cannabinoids.

**Pharmacodynamic interactions:** The simultaneous administration of hypnotics, sedatives or other drugs that have a sedative effect can lead to an additive effect of sedation and muscle relaxation caused by THC. Of major importance are also interactions with drugs exerting effects on the cardiovascular system. Pharmacodynamic interactions may also be of therapeutic value. Thus, THC and opiates show synergistic properties in pain relief, which can be used to reduce the dose of opiates. Such desired pharmacodynamic interactions and synergies could also be observed in combination with other drugs.

**Acute side effects:** The acute side effects caused by cannabis use are mainly related to psyche and cognition and to circulation with euphoria, anxiety, changes in sensory perception, impairment of memory and psychomotor performance being common effects after a dose is taken that exceeds an individually variable threshold. Acute cannabis consumption may increase heart rate and change blood pressure, which may have serious consequences in people with heart disease.

**Long-term side effects:** Effects of chronic use may be induction of psychosis, development of dependency to the drug, and impairment of cognitive abilities, the latter being reversible after abstinence, except possibly in very heavy users. Due to the higher sensitivity of the fetal and the adolescent brain to the drug the use by young people has more detrimental effects than use by adults and cannabis exposure in utero may have negative consequences on cognitive abilities in later life. Use of moderate doses in a therapeutic context by adults is usually not associated with severe side effects justifying medical uses of cannabis for a range of severe illnesses. Current prohibition on cannabis use may also have harmful side effects for the individual patient and the society. For example, patients suffering from many chronic illnesses, which could be treated with cannabis-based medicines, have an increased likelihood for suicide.
Since March 2017, following an amendment of the German Social Security Statute Book (SGB V §31 Abs. 6), cannabinoids can be prescribed in Germany under statutory health insurance regulations if specific patient conditions apply. In particular, patients must prove to health insurance carriers that (1) they suffer from a severe disease and (2) that they have reached the end of reasonable options from conventional therapy, or that such options cannot be made use of for other clear medical reasons. Statutory health insurance carriers almost always engage the Medical Service of the Health Funds (MDK) to precisely inspect such applications, resulting in an approval rate of approximately 60% according to recent numbers. Private medical insurance carriers and state aid authorities usually follow similar approaches.

For accompanying physicians the application process usually results into substantial unpaid work-time and into several uncertainties/worries, i.e. related to practice budgets, recourse claims, legal issues etc., making it rather unappealing to support such issues, largely due to non-medical reasons. Independent from Social Law, cannabinoids can be prescribed by physicians to patients based on German narcotics law (§ 13 BtMG) independently from reimbursability issues. While being less restrictive to some extent, such prescriptions (which have to be paid fully by the patients) still require a sound medical justification, explaining why non-narcotic therapeutic options could not be applied instead. In 2019 the German SGB „Cannabis Law“ was amended, making it easier to now change between different cannabinoid medicines and reducing statutory health insurance processing times in hospital contexts.

Overall, from the medical perspective the current legal situation for Cannabis treatments in Germany is a positive development on one hand by opening up new therapeutic options; on the other hand several uncertainties and obscurities remain and will have to be resolved in the coming years in order to further clarify the place of cannabinoids in the German health care system.
From 1964 when Raphael Mechoulam isolated and synthesized tetrahydrocannabinol, it has been the primary focus of cannabis research. More recently, the synergistic contributions of cannabidiol to its pharmacology and analgesic medicinal value have been demonstrated (1). Other phytocannabinoids including tetrahydrocannabivarin, cannabinol, tetrahydrocannabinolic acid and cannabidiolic acid harbour additional effects of therapeutic interest. Innovative conventional plant breeding has yielded cannabis chemotypes expressing high titres of each component for future study.

The cannabis terpenoids provide another echelon of phytotherapeutic agents (2-4): limonene, α-pinene, linalool, β-caryophyllene, et al. These half-siblings of phytocannabinoids are all flavour and fragrance components common to human diets that have been designated Generally Recognized as Safe (GRAS) by the US Food and Drug Administration and other regulatory agencies. Terpenoids are quite potent, and affect animal and even human behaviour when inhaled from ambient air, at serum levels in the single digits ng/ml. They display unique therapeutic effects that may contribute meaningfully to the entourage effects of cannabis-based medicinal extracts.

Cannabis has acquired a public opinion as a miracle drug that has not yet been supported by randomized clinical trials. However, it has proven extremely versatile in treatment in a wide variety of otherwise recalcitrant disorders through modulation of the endocannabinoid system (ECS). The scientific rationale will be presented from basic science research, available clinical data, and prospective formulation of cannabis-based medicines to treat brain tumors, Alzheimer disease, traumatic brain injury (post-concussion syndrome) (5), and endometriosis (6), all disorders where “conventional medicine” has failed to produce acceptable results.

In just a few years, cannabidiol (CBD) has become immensely popular around the world. After initially being discovered as an effective self-medication for Dravet syndrome in children, CBD is now sold and used to treat a wide range of medical conditions and lifestyle diseases. The cannabinoid CBD, a non-psychoactive isomer of the more infamous tetrahydrocannabinol (THC), is available in a growing number of administration forms, but the most commonly known is CBD oil. There are currently hundreds, if not thousands, of producers and sellers of CBD oils active in the market, and their number is increasing daily. Those involved vary from individuals who prepare oils on a small scale for family and (Facebook) friends to compounding pharmacies, pharmaceutical companies, and licensed cannabis producers.

Despite the growing availability of CBD, many uncertainties remain about the legality, quality, and safety of this new “miracle cure.” As a result, CBD is under scrutiny on many levels, ranging from national health organizations and agricultural lobbyists to the WHO and FDA. The central question is whether CBD is simply a food supplement, an investigational new medicine, or even a narcotic. This presentation looks into the known risks and issues related to the composition of CBD products, and makes recommendations for better regulatory control based on accurate labeling and more scientifically supported health claims. The intention of the presentation is to create a better understanding of the benefits versus the risks of the current way CBD products are produced, used, and advertised.
CANNABIS, CANNABINOIDS, AND THE OPIOID EPIDEMIC

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Introduction: Opioids are a primary contributing factor in substance related overdose deaths. As such, novel pharmacotherapeutic strategies are urgently needed to curb reliance on opioids for pain relief. This presentation will explore several lines of evidence from preclinical investigations to population-based studies suggesting that cannabinoids and other cannabis constituents may have a role in decreasing or eliminating opioid use for pain management. For instance, self-report data and some US state-level findings have pointed to the possibility that cannabis may decrease opioid use in pain patients. However, data from controlled investigations probing the potential of cannabis and cannabinoids to decrease the amount of opioids needed to control pain are limited. Findings and ongoing studies from our laboratory will be highlighted.

Methods: Using double-blind, placebo-controlled methods, we are investigating cannabis and cannabinoid modulation of opioid analgesia, intoxication, and abuse liability. Healthy, cannabis smokers participate in these outpatient studies and analgesia is assessed using a well-validated elicited pain test, the Cold Pressor Test (CPT). A completed study investigating the effects of cannabis with delta-9-tetrahydrocannabinol (THC) on dose-dependent opioid analgesia will be presented. An ongoing study examining the impact of cannabis with varying concentrations of THC and cannabidiol (CBD) on opioid analgesia will also be discussed.

Results: Alone, cannabis produced non-significant increases in analgesia, and significantly increased ratings of intoxication and abuse liability. The low dose of the opioid tested also failed to produce analgesia when administered alone. However, this opioid dose elicited significant and robust analgesia when combined with cannabis without affecting cannabis’s abuse liability or intoxication.

Conclusion: Some population-level and self-report findings point to the possibility that cannabinoids may serve as a substitute or adjunct to opioids for pain relief. Early controlled clinical studies confirm the potential for cannabis to enhance opioid analgesia, supporting THC-opioid synergy observed in preclinical investigations. In addition to THC, other cannabis constituents including CBD and specific terpenes may similarly reduce or eliminate reliance on opioids for pain relief.

This research was supported by the US National Institute on Drug Abuse Grant DA009236, and DA027755, DA046614
As a pediatric cannabis specialist in Los Angeles, Dr. Goldstein has evaluated over 900 ill children for the use of medical cannabis. She will discuss her clinical experience including mechanisms of action of cannabinoids for epilepsy and autism, as well as her patients results and clinical pearls. She will also discuss dosing for pediatric conditions.
THE MEDICAL USE OF CANNABIS IN ELDERLY

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Cannabinoid use is of particular interest for older individuals who may experience symptoms such as chronic pain, sleep disturbance, cancer-related symptoms and mood disorders, all of which are often poorly controlled by current drug treatments that may also incur medication-induced side effects. The trend among seniors using medical marijuana is on the up-and-up: in recent years, cannabis use among seniors increased by 300 percent. However, the risk of known and potential adverse effects is considerable, with concerns for cognitive, cardiovascular and gait and stability effects in old adults. Nevertheless, most research suggest that medical cannabis may be safe and effective in the treatment of a wide range of chronic symptoms related to various illnesses in elderly patients. It was repeatedly shown, that careful controlled cannabis use may decrease the use of other prescription medicines, including opioids. Gathering more practice-based data, creating registries collecting real-world data on many aspects of medical cannabis use, initiation more naturalistic, proof-of concept and controlled studies, in this special population is imperative.

Literature References:


Dr. Mark A. Ware
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The relief of pain has widely been recognised as the most common reason for medical use of cannabis worldwide. Along with other chronic symptoms such as anxiety and insomnia, poor symptom management remains a global challenge, with pharmaceutical options remaining limited in efficacy and tolerability, and non-pharmacological options limited by accessibility and This is largely a patient-driven phenomenon as cannabis has been challenging to study in formal clinical trials, for a variety of reasons, and the scientific evidence lags behind the patient experience. This presentation will explore the challenges in evaluating the safety and efficacy of the use of cannabis for pain, including the different cannabinoids and their ratios, different types of pain, novel clinical research methodologies and study designs. We will explore future directions in the study of cannabinoids and pain management, including alternative delivery systems and formulations. The role of the medical use of cannabis as a factor in the opioid crisis will be discussed from different perspectives.
CANNABINOIDS IN DERMATOLOGY: A “HIGH” WAY TO HEAL?

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The endocannabinoid system (ECS) has lately been proven to be an important, multifaceted homeostatic regulator, which influences a wide-variety of physiological processes all over the body. Its members, the endocannabinoids (eCBs; e.g. anandamide), the eCB-responsive receptors (e.g. CB1, CB2), as well as the complex enzyme and transporter apparatus involved in the metabolism of the ligands were shown to be expressed in several tissues, including the skin. Although the best studied functions of the ECS are related to the central nervous system and to immune processes, experimental efforts over the last two decades have unambiguously confirmed that cutaneous cannabinoid (“c[ut]annabinoid”) signaling is deeply involved in the maintenance of skin homeostasis, barrier formation and regeneration, and its dysregulation was implicated to contribute to several highly prevalent diseases and disorders, e.g. atopic dermatitis, psoriasis, scleroderma, acne, hair growth and pigmentation disorders, keratin diseases, various tumors, and itch. The current lecture aims to give an overview of the available skin-relevant endo- and phytocannabinoid literature with a special emphasis on the putative translational potential, including ongoing clinical trials, and to highlight promising future research directions as well as existing challenges.


Acknowledgements: NRDIO 121360, and 125055; János Bolyai Research Scholarship of the Hungarian Academy of Sciences, and “Bolyai+ Scholarship” of the New National Excellence Program of the Ministry of Human Capacities (ÚNKP-19-4-DE-287).
The success of new drugs depends on our ability to understand their molecular and cellular mechanism of action. Modulation of cannabinoid CB1 and CB2 receptors activity by endogenous lipid messengers, termed endocannabinoids, is associated with therapeutic benefits in humans. Poor understanding of the physiological role of endocannabinoids and lack of detailed selectivity profiling of experimental drugs, however, led to the market withdrawal of Acomplia®, a CB1 receptor antagonist, and the death of one volunteer in a phase 1 clinical trial exposed to the FAAH inhibitor BIA 10-2474. In this lecture I will introduce the endocannabinoid system and discuss recent progress to exploit this system for therapeutic benefit.
The incidence of neurodegenerative disorders has significantly increased in the past 50 years in parallel to the elevation in life span, in particular in developed countries. This increase will persist in coming years, so that, in 2030, the world population will be 2-fold higher with highest increases concentrated in subjects over 65 years. This will give neurodegenerative disorders much more opportunities to be visible, demanding neuroprotective and neurorepair therapies, whose development has remained elusive in the last 20-30 years. Among the numerous therapeutic properties investigated for cannabinoids, neuroprotection is one of the most promising.

Cannabinoids have demonstrated to be active in the preservation, rescue, repair and/or replacement of neural cells against a myriad of insults that deteriorate their homeostasis and integrity. Such important properties are possible by the location of druggable targets for cannabinoids (e.g. CB₁, CB₂, GPR55 and PPAR receptors; FAAH and MAGL enzymes) in CNS structures (e.g. blood-brain barrier (BBB)) and cellular substrates (e.g. neurons, astrocytes, reactive microglia, oligodendrocytes, and their precursor cells) that are critical in cell degeneration, protection, and repair, then enabling cannabinoids to positively control these functions.

For example, the CB₁ receptor is located in: (i) glutamatergic neurons where it controls the excessive glutamate release limiting excitotoxic damage; (ii) astrocytes where it contributes to glutamate clearance and enhances the metabolic support exerted by these cells on neurons; (iii) neural progenitors cells where it promotes their maturation facilitating repair processes; and (iv) the BBB where it improves vascular supply and limits peripheral cell infiltration. This is also happens with the CB₂ receptor, which is preferentially located in reactive microglial cells and, in some diseases, in activated astrocytes, so that the activation of this receptor downregulates the synthesis of proinflammatory molecules, while enhancing the production of prosurvival mediators. Such beneficial effects may be also elicited by targeting GPR55 and PPAR-γ receptors, both expressed in microglial cells and being able to regulate the toxicity exerted by these cells on neurons.

In summary, the relevance of active targets for cannabinoids places this family of pleiotropic compounds in a promising position for developing novel neuroprotection- and neurorepair-based therapies. Benefits should be obtained with cannabinoids having a broad-spectrum profile or combinations of compounds, an objective essential in neurodegenerative disorders, in which neuronal damage is the result of a concerted action of neurotoxic events, demanding a multi-target strategy able to limit all these processes in a coordinated manner.

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

In this presentation I will discuss these issues and also other possible future studies that may help to clarify whether cannabinoids may be useful as anticancer agents in patients with gliomas or other cancers.
The psychoactive constituent of cannabis, delta-9-tetrahydrocannabinol, produces its pharmacological effects by activating cannabinoid receptors in the brain and peripheral organs. The two primary endogenous ligands for these receptors are the lipid-derived transmitters, anandamide and 2-arachidonoylglycerol (2-AG). Anandamide and 2-AG are released in select regions of the brain and throughout the periphery of the body, and are deactivated via a two-step process consisting of transport into cells followed by intracellular hydrolysis. Anandamide hydrolysis is catalyzed by fatty-acid amide hydrolase (FAAH), while 2-AG hydrolysis is primarily mediated by monoacylglycerol lipase (MGL). In my talk, I will provide a brief outline of drug classes that selectively interfere with the deactivation of anandamide and 2-AG, focusing on their pharmacological properties and therapeutic potential. Two decades of basic science and clinical research point to these agents as promising therapeutic candidates for the treatment of human pathologies such as pain, addiction, anxiety and post traumatic stress disorder.
CANNABIDIOL IN NEUROPSYCHIATRY: BEST LEADING OR SUPPORTING ACTOR?

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The Cannabis sativa plant contains more than a hundred chemical compounds with similar chemical structures, known as cannabinoids. The principal psychoactive constituent in cannabis is Δ9-THC, responsible for the significant effects related to the use of the plant. Among the many other cannabinoids, our Brazilian research group has focused on cannabidiol (CBD), a compound that does not yield the classical subjective effects of marijuana. Since the 1970s, our group has produced many scientific articles showing the possible therapeutic results of CBD in different animal models of neuropsychiatric disorders, as well as in preliminary clinical trials with humans.

Methods: The present review aims to report the main contributions for the development of the therapeutical potential of CBD in neuropsychiatry, primarily performed by Brazilian researchers, which helped to transform the view of CBD from an inactive cannabinoid to medicine with multiple actions. The studies included here were selected based on searches performed in the online databases PubMed, Web of Science, and ScieELO for papers dealing with the therapeutic applications of CBD (“cannabidiol” was used as a keyword).

Results: We were the pioneers to demonstrate the anxiolytic and antipsychotic effects of CBD in animals, in the 1970s and 1980s, and later in clinical patients, with rather promising results. In addition to anxiety and psychosis, basic and clinical research on other therapeutic possibilities of CBD was conducted, such as Parkinson’s and sleep disorders. Moreover, patentable synthetic analogs of CBD with strong potential for knowledge transfer to the productive sector have recently been developed to offer the possibility of benefits for patients with many health conditions.

Conclusions: CBD has shown to be a useful and promising compound that may help patients with diverse clinical conditions. Double-blind, placebo-controlled clinical trials with different neuropsychiatric conditions in larger populations that are currently under investigation should bring essential clues shortly and support the translation of research findings to clinical settings. The possible interactions with other drugs, safety, and side effect profile, as well as the therapeutic window for each clinical condition, should be determined.
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Brain tumours are the leading cause of cancer-related death in children and are among the most challenging childhood cancers to treat. Medulloblastoma is the most common malignant brain cancer of childhood. Surgical resection followed by radiotherapy and chemotherapy are the mainstays of frontline treatment. The overall survival rates for medulloblastoma patients have not improved for decades, and the impact of the current treatment is devastating, producing long-term sequelae in survivors. Thus, there is an urgent need to identify more effective therapeutic strategies for medulloblastoma that have potential to improve survival rates and reduce treatment-related toxicity. A large body of evidence has demonstrated that cannabinoids, the active compounds of the plant Cannabis sativa, exert anti-tumour actions in different cancer types. Moreover, it has been shown that cannabinoids can improve the effect of chemotherapy and radiotherapy in glioblastoma models. Although there is growing evidence about the anti-tumour properties of cannabinoids in adult cancers, there is very little data about their effect on paediatric tumours. In particular, there is no existing data in paediatric brain tumour models. In this context, we aimed to determine if cannabinoids, both pure compounds and whole plant extracts, have anti-tumour efficacy on paediatric brain tumours either alone and in combination with conventional chemotherapies.

**Methods:** Three patient derived group 3 medulloblastoma cell lines were used (D425, D283 and PER547). Compounds: pure Δ⁹-tetrahydrocannabinol (THC) and cannabidiol (CBD), whole plant extracts (WPE) rich in THC and CBD. Alamar blue was used to measure cell survival in the viability assays and drug interaction assays. Then, computational algorithms were used to determine if the anti-proliferative effect of the combination treatments was enhanced over single drug treatments. The ED50 was used to study autophagy and apoptosis signalling pathways at different timepoints after treatment. CB1 and CB2 expression was analysed in public databases (‘R2: Genomics Analysis and Visualization Platform (http://r2.amc.nl)”) and by qPCR in paediatric brain tumour samples.

**Results:** Here we show that different paediatric brain tumour types express both cannabinoid receptors, CB1 and CB2. We further investigated the effects of cannabinoids in medulloblastoma cells and show that pure THC, pure CBD, WPE-THC and WPE-CBD reduce the viability of these cells. This effect is mediated, at least in part, by CB2 and by the production of reactive oxygen species. Furthermore, cannabinoids induce autophagy and apoptosis in medulloblastoma cells. Additionally, cannabinoids interact in an additive manner with conventional chemotherapeutics cyclophosphamide and gemcitabine.

**Conclusion:** These results suggest that cannabinoids could be an interesting therapeutic tool for the management of medulloblastoma. Current work is investigating the therapeutic potential of these agents using preclinical models.
ABX-1431, A FIRST-IN-CLASS ENDOCANNABINOID MODULATOR, IMPROVES TICS AND THE URGE TO TIC IN ADULT PATIENTS WITH Tourette Syndrome

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Introduction: Tourette syndrome (TS) is a neurodevelopmental disorder characterized by motor and vocal tics with onset in childhood. Based on an increasing number of case series, it has been suggested that exocannabinoids including cannabis, cannabis extracts, and dronabinol might improve tics and associated psychiatric comorbidities in otherwise treatment resistant patients with TS. Results from two small randomized placebo-controlled trials provided further evidence by demonstrating a significant tic reduction after treatment with dronabinol. Based on this clinical data, an involvement of the endocannabinoid system (eCB) has been suggested in TS. For stimulation of the eCB system not only exocannabinoids can be used, but also substances that inhibit the degradation of the endocannabinoids anadamide and 2-arachidonoylglycerol (2-AG). ABX-1431 is a first-in-class, oral, highly selective inhibitor of the enzyme monoacylglycerol lipase (MGLL) that raises nervous system concentrations of 2-AG. 2-AG acts not only as an agonist on presynaptic central cannabinoid (CB1) receptors, but also exerts feedback inhibition on neurotransmitter release. Since MGLL is abundant in the basal ganglia - a brain area that is suggested to be involved in the pathology of TS - we hypothesized that ABX-1431 may improve tics and psychiatric comorbidities in patients with TS.

Methods: 20 adult patients (16 men, 4 women, mean age ± SD = 34 ± 11 years, range, 18-54 years) with moderate-severe TS were treated in a single-dose crossover study with 40 mg ABX-1431 or placebo. Endpoints were tic severity according to the Yale Global Tic Severity Scale Total Tic Score (YGTSS-TTS), the Modified Rush Video-Based Tic Rating Scale (MRVS), and the self-assessment Adult Tic Questionnaire (ATQ), and premonitory urges according to the Premonitory Urge for Tics Scale (PUTS).

Results: Patients displayed a placebo-adjusted ABX-1431-related tic improvement in the YGTSS-TTS at 8 hours (p=0.0384), with improvement in motor tics at 4 hours (p=0.0016) and 8 hours (p=0.0049), and a reduction in self-reported tic intensity (ATQ) at 4 hours (p=0.0005) and 8 hours (p=0.0008). A placebo-adjusted ABX-1431-related improvement in premonitory urges was observed at 4 hours (PUTS, p=0.0369), while no significant difference was observed with the MRVS. The most common adverse events were headache, somnolence, and fatigue, which resolved.

Conclusions: ABX-1431 is a specific inhibitor of the major clearance pathway of the primary endocannabinoid in the human brain 2-AG. From our data it is suggested that modulation of the eCB system by selective inhibition of MGLL using ABX-1431 improves tics and the urge to tic in adult patients with TS. ABX-1431 was well tolerated and caused no serious adverse events. ABX-1431, therefore, may provide a unique treatment profile for the treatment of patients with TS. Furthermore, it holds promise as a novel mechanism to treat also patients with other movement disorders as well as neuropsychiatric conditions.
MEDICAL CANNABIS FOR OLDER PATIENTS – TREATMENT PROTOCOL AND INITIAL RESULTS

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Background: Older adults may be able to benefit from cannabis treatment for various symptoms such as chronic pain, sleep difficulties, reduced appetite and others, that are not adequately controlled with evidence-based therapies. However, currently there is a dearth of evidence about the efficacy and safety of cannabis treatment for these patients. The aim of this study is to present a pragmatic treatment protocol for medical cannabis in older adults.

Methods: Prospective follow-up of consecutive patients above 65 years of age who are treated with medical cannabis within a geriatric specialized clinic from April 2017 to October 2018. The outcomes included treatment adherence and adverse events after six months of treatment. A review of the literature for efficacy and safety of cannabis treatment also was performed.

Results: During the study period, 184 patients began cannabis treatment, 83.2% of them were 75 years of age or older and 63.6% were female. After six months of treatment, 58.1% were still using cannabis. Of these patients, 33.6% reported adverse events, the most common of which were: dizziness (12.1%), sleepiness and fatigue (11.2%). Robust evidence of cannabis efficacy is overall scanty, but potential indications include pain, sleep disturbances, nausea and vomiting, Parkinson’s disease, post-traumatic stress disorder, dementia and palliation. Special caution is warranted in older adults due to polypharmacy, pharmacokinetic changes, nervous system impairment and increased cardiovascular risk.

Conclusion: Medical cannabis should still be considered carefully and individually for each patient after a risk-benefit analysis and followed by frequent monitoring for efficacy and adverse events.
A PHASE II, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL TO INVESTIGATE THE EFFICACY AND SAFETY OF AVIDEKEL OIL FOR THE TREATMENT OF PATIENTS WITH AGITATION RELATED TO DEMENTIA

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Introduction: The most common syndrome in patients with severe dementia is agitated behavior. The treatment options for this syndrome are limited and lead to severe side effects. In vivo trials on animals and clinical studies on adults show that cannabinoids (CBD) could have a beneficial effect on behavioral disorders in general, and in dementia-related disorders in particular. The aim of this phase II, randomized, double blind, placebo-controlled, 2-arm trial, was to evaluate the safety and efficacy of CBD rich whole plant oil for the treatment of subjects with agitation related to dementia.

Methods: 64 patients were randomly assigned in a 2:1 ratio to receive Avidekel Oil or placebo respectively. Patients received the oils as drops applied under the tongue 3 times a day. Over the course of sixteen weeks (112 days), ten visits were conducted approximately every two weeks. In each visit the following relevant variables were collected: Physical Examination, Vital Signs- temperature, pulse, blood pressure, height (only screening visit) and weight, Behavioral Disorders assessment based on the Cohen-Mansfield Agitation Inventory (CMAI), Neuropsychiatric Inventory (NPI-NH), Clinical Global Impression Severity- Agitation / Aggression (CGI-S-A/A), Mini-Mental State Examination (MMSE), Concomitant Medications, Adverse Events, Mood based on the GDS questionnaire, Safety Tests- Hematology panel and Chemistry panel.

Preliminary results: A total of 64 eligible patients were screened and recruited for this trial. Their average age at screening was 79 with 37.5% men. Four patients withdrew before randomization due to a change in their medical condition, 60 patients began cannabis / placebo treatment, 40 in the active treatment group and 20 in the control group. Selective data related to the efficacy of Cannabidiol as a treatment for the agitation related to dementia will be presented.
CANNABIS INDUCES CLINICAL RESPONSE BUT NO ENDOCSPIC RESPONSE IN CROHN’S DISEASE PATIENTS

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Introduction: Many patients with Crohn’s disease (CD) report that the use of medical cannabis improves their symptoms, however studies evaluating objective disease parameters such as inflammatory markers and endoscopic score are lacking. We aimed to assess the effect of cannabis on Crohn’s disease patients.

Methods: In a double blind, randomized placebo-controlled trial patients received either cannabis oil with 15% Cannabidiol (CBD) and 4% tetrahydrocannabinol (THC) or placebo for eight weeks. Parameters of disease including Crohn’s disease activity index (CDAI), C reactive protein (CRP), calprotectine, simple endoscopic score for Crohns disease (SES-CD) and quality of life (QOL) were assessed before, during and after treatment. Seven patients at the open label phase were invited to PK examination after at least 12 hours without cannabis. Blood samples were taken at time 0 and then all participants received the same dose of cannabis oil (4 drops, each drop contain 6 mg CBD and 1.5 mg of ∆9-THC). We took blood samples after 15 minutes, 30 minutes, 45 minutes, 60 minutes, 90 minutes, two hours, three, four, five and six hours. We found that after 90 minutes We performed an in-depth analysis of the cannabinoids and terpenoids composition in the product given to patients.

Results: The study included 46 patients, 31 males (62%), 23 in each group. Average age was 35±12. CDAI before the treatment was 288.4±78.0 and 298.5±112.2 after eight weeks of treatment the CDAI was 143.1±96.0 and 209.5±113.0 in the cannabis and placebo groups, respectively (p<0.05). Remission (CDAI <150) was achieved in 65% of the cannabis group and 35% of the placebo group. Median quality of life score after 8 weeks was 90.1(IQR 83-102) in the cannabis group and 76 (IQR 68-92) in the placebo group (p<0.05). SES-CD was 9.5±6.5 and 11.9±6 before treatment and 7.17±6 and 9.8±5.4 after treatment in the cannabis and placebo groups, respectively (p=0.17). The THC and CBD levels in the participants’ blood reached a peak of almost 2.5 ng/mL of THC and 6 ng/mL of CBD in average.

Conclusions: Eight weeks of CBD reach Cannabis treatment induced significant clinical improvement but no change in inflammatory parameters or endoscopic score. Oral cannabis oil seems to absorb well and reach blood therapeutic level. Until further studies are available, cannabis treatment in Crohns disease should be reserved either for temporary symptom relief until remission is achieved, or for sever refractory disease.
TOPICAL MEDICAL CANNABIS-BASED MEDICINES (TCBM): A NEW EPIGENETIC PARADIGM FOR INTEGUMENTARY & WOUND MANAGEMENT

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The endocannabinoid system is ubiquitous throughout the human body and has recently been found to have a significant representation throughout the integumentary system (cutaneous membranes and mucous membranes). It has been postulated that dysregulation of endocannabinoid tone is a dominant driver of many integumentary and wound conditions. Topical Cannabis-Based Medicines (TCBM) may contain both delta-9-tetrahydrocannabinol (THC) and Cannabidiol (CBD) in varying proportions. The lipophilic nature of diseased integument and wounds is an ideal environment for the topical application of lipophilic molecules including cannabinoids.

Methods: An open label trial was conducted on a cohort of chronically ill elderly patients with non-healing complex recalcitrant wounds. The pre-treatment wound duration ranged between 6 months and 11 years. All cases were previously afforded all available Evidence-Based treatments that conformed with local best practices and wound-bed preparation principles. The cohort studied comprised a total of 30 patients with over 40 wounds. Twenty-eight patients were affected with cutaneous membrane lesions, and 2 patients had mucous membrane lesions. Twenty-seven patients had lesions on their lower limbs, 2 involved the head and neck region, and one had genital lesions. Etiologies represented within the cohort under study included: pyoderma gangrenosum, psoriasis, pressure injuries, arterial leg ulcers, venous leg ulcers, diabetic foot ulcers, calciphylaxis (uremic and non-uremic), leukocytoclastic vasculitis, cryoglobulinemia, antiphospholipid syndrome, sickle cell disease, lichen simplex chronicus, Bowen’s Disease, and Squamous Cell Cancer. TCBM was applied directly to wound beds, wound edges, and peri wound areas, once every 1 or 2 days.

Results: Complete healing was documented in almost 90% of wounds. The time interval to complete wound closure ranged between 3 weeks to seven months. Clinically significant analgesia and opioid-sparing effects were also documented. Decreased utilization of systemic antibiotics was also noted. TMC based medicines were very well tolerated and no adverse reactions, neither local nor systemic, were observed. At least 4 patients had been offered limb amputation prior to entering the study, yet no patients underwent amputation.

Conclusions: The highly positive results observed in a cohort of the most challenging recalcitrant wounds affecting the most compromised patients provokes realistic interpolation that TCBM may be effective for a broader context within Integumentary and Wound Management. Given its extracellular and intracellular duality, the endocannabinoid system is theorized to be a viable epigenetic target and platform for exploring novel therapeutic options for integumentary and wound conditions. Thus, novel therapies involving TCBM possess significant potential to improve the 3 main target outcomes within integumentary and wound management, namely, wound healing, wound analgesia, and disease modulation that includes antineoplastic activity.
CANNABIS SIGNIFICANTLY REDUCES THE USE OF OPIOIDS & IMPROVES QUALITY OF LIFE IN PATIENTS;
RESULTS OF A LARGE PROSPECTIVE STUDY

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Background: This presentation will examine the findings from Canada’s largest national longitudinal examination medical cannabis patients, with a focus on the impacts of cannabis use on prescription opioids and quality of life over a 6 month period.

Methods: The Tilray Observational Patient Study (TOPS) is taking at 21 different medical clinics in 5 provinces throughout Canada. This analysis includes 1145 patients enrolled at/before October 15 2018 that had at least one post-baseline visit. Detailed baseline characteristics were gathered in person on REDCap via iPad during an initial patient clinic visit, with follow up at 1, 3, and 6 months. A comprehensive cannabis use inventory and the World Health Organization Quality of Life Bref (WHOQOL-BREF) were self-administered by patients during clinic visits, and a detailed prescription drug questionnaire was completed by health care providers at each visit.

Findings: The sample is 42.4% male (n=485) with a mean age of 51.2 (SD=15.4), and the top 3 symptoms reported by participants were chronic pain (79.9%; n=915), insomnia (33.5%; n=384), and anxiety (28.6%; n=327). Mean cannabis use per week was 6.5gms per week at 1 month, and the most common method of use was oral ingestion (54.9%; n=628), followed by joints (22%; n=252) and vaporization (14%; n=160). All 4 domains of the WHOQOL-Bref – physical health, psychological health, social relationships, environment – saw statistically significant improvements between baseline and month 6, with the most significant changes seen in physical health (13.9 points/26.4% increase [95% CI = 11.7, 15.0]) and psychological health (9.2 points/14.4% increase [95% CI 6.6, 9.7]). Baseline opioid use was reported by 28.1% (n=313) of patients, dropping to 11.3% of total study participants at 6 months. Mean mgs. per day opioid use among patients using opioids at baseline that completed a 6 month follow-up dropped from 152mgs per day at baseline to 32.2mgs per day at 6 months, a 78% reduction in mean opioid dosage.

Discussion: While cannabis substitution effect for prescription drugs has been identified and assessed via cross-sectional and population level research, this study provides a granular individual-level perspective of cannabis substitution for opioids and other prescription drugs and associated improvement in QOL over time. The high rate of cannabis use for the treatment of chronic pain and subsequent substitution for opioids suggests that cannabis may play a harm reduction role in the ongoing opioid dependence and overdose crisis, and improve the quality of life of patients.
AN EXPERIMENTAL RANDOMIZED TRIAL ON THE ANALGESIC EFFECTS OF PHARMACEUTICAL-GRADE CANNABIS IN CHRONIC PAIN PATIENTS WITH FIBROMYALGIA

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Introduction: Given the growing number of chronic pain patients on opioid treatment and the associated addiction epidemic in both the US and Europe, effective pain treatment alternatives may possibly be found in the use of cannabis. In this experimental randomized placebo-controlled 4-way crossover study, we investigated the analgesic effects of inhaled pharmaceutical-grade cannabis.

Methods: We studied four different cannabis varieties with specific knowledge on their Δ9-tetrahydrocannabinol (THC), and cannabidiol (CBD) content: Bedrocan® (22.4 mg THC, < 1 mg CBD), Bediol® (13.4 mg THC, 17.8 mg CBD), Bedrolite® (18.4 mg CBD, < 1 mg THC) and a placebo variety without any THC or CBD. Twenty chronic pain patients with fibromyalgia inhaled a single cannabis dose, after which arterial blood samples were obtained to measure THC and CBD plasma concentrations, pressure and electrical pain thresholds, spontaneous pain scores and drug high were measured for 3 hours.

Results: None of the treatments had an effect greater than placebo on spontaneous or electrical pain responses, although more patients receiving Bediol® displayed a 30% decrease in pain scores compared to placebo (90% vs. 55% of patients, p = 0.01), with spontaneous pain scores correlating with the magnitude of drug high (ρ = -0.5, p < 0.001). Cannabis varieties with THC caused a significant increase in pressure pain threshold relative to placebo (p < 0.01). CBD inhalation increased THC plasma concentrations but decreased THC-induced analgesic effects, indicative of synergistic pharmacokinetic but antagonistic pharmacodynamic interactions of THC and CBD.

Conclusion: This experimental study shows the complex behavior of inhaled cannabinoids in chronic pain patients with small analgesic responses following a single inhalation. Further research is needed to determine long-term treatment effects on spontaneous pain scores, THC-CBD interactions and the role of psychotropic symptoms on pain relief.
CHARACTERISTIC OF MEDICAL CANNABIS CONSUMPTION AMONG FIBROMYALGIA PATIENTS

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Introduction: Medical cannabis (MC) is becoming more and more popular among patients with chronic pain syndromes. It reduces pain and muscle spasm, induces sleep, improves tiredness, anxiety and depression. In this study we evaluated the characteristics of MC use among patients with fibromyalgia.

Methods: All patients with fibromyalgia who were followed up at Laniado hospital in Netanya and at the Nazareth Hospital in Nazareth, and treated with medical cannabis were located and contacted. These patients were asked regarding MC use, including method of use, frequency, monthly consumed amount, growing company, current and previously used cannabis species, percent of tetrahydrocannabinol (THC) and cannabidiol (CBD), dominance of Sativa or Indica of the current medical cannabis species, buying medical cannabis from the black market, use during work, current use of other pain killers, impact of medical cannabis on clinical parameters like pain, sleep, anxiety, depression, blood pressure, glucose levels, capability of work, leisure time outside home, travelling, driving, giving other people from their own cannabis and adverse effects of cannabis.

Results: One-hundred and one patients completed the study. 73% of the participants were female with a mean age of 45±11.8 years. Mean duration of cannabis consumption was 15.3±12.6 months and mean monthly consumption amount was 28.6±10.2 grs. Mean THC % of MC used during day time was 16.4±3.3 (9.3-20) and during night time 19±6.6 (12-28). Mean CBD % of MC used during day time was 2.66 ±4.6 (0.1-13.9) and during night time 0.65±0.62 (0.1-2). 54% smoked pure cannabis, 18% used vaporized cannabis only, and 3 participants used cannabis oil only. The rest used a variety of combinations. Mean daily minimal frequency of MC consumption was 4.11±2.9 times and mean maximal daily consumption was 7.9±5.6 times. Mean no. of current daily MC species was 2.11±1 and mean no. of tried species was 6.7±5.2 for each participant. 47% of all the participants stopped any other treatment for fibromyalgia and a similar figure reduced the consumed amount of other treatments. Mean level of improvement, compared to baseline, in sleep and pain was slightly more than 77% with less improvement in other parameters. 36% of the patients reported weight gain, while 16% reported weight loss. 51% reported having more leisure time outside their homes. Nearly all patients refused sharing any amount of their cannabis with friends or family members and all patients recommended cannabis for their loved ones, once they develop severe fibromyalgia. Nearly one quarter of the patients reported mild adverse effects and one patient developed a psychotic attack (patient with lupus also, consuming 70 gram of MC monthly).

Conclusions: MC is an effective treatment for fibromyalgia, with nearly 0% withdrawal from the treatment. Mean daily consumed amount was less than 1 gram and the main method of consumption was smoking with huge variety of the frequency of smoking during day and night time, among the participants. Relatively few patients used cannabis oil. Experienced MC consumers used relatively a large no. of MC species during the day. All participants recommended cannabis for their loved ones in case they develop severe fibromyalgia. Mild adverse effects were reported in nearly a quarter of the patients but did not result in discontinuing its consumption.
USE OF CANNABIS TO RELIEVE PAIN AND PROMOTE SLEEP BY CUSTOMERS AT AN ADULT USE DISPENSARY

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Background: Medical cannabis patients consistently report using cannabis as a substitute for prescription medications, including analgesics and sleep aids. However, little is known about customers accessing cannabis through adult-use markets. The aim of this study was to examine the use of cannabis for symptom relief and the substitution of cannabis for prescription and over-the-counter analgesics and sleep aids among customers at adult use dispensaries.

Materials and Methods: A survey at two retail stores within a single dispensary organization was conducted. Between August 2016 and October 2016, store staff asked customers if they wanted to participate and, if so, provided an electronic link to the survey. All customers reporting medical certification were excluded.

Results: A total of 1,000 unique adult-use only customers responded. Most (90%) were under the age of 50, with 42% women and 66% reporting white, non-Hispanic race/ethnicity. Of all respondents, 65% reported taking cannabis to relieve pain and 74% reported taking cannabis to promote sleep. Among respondents taking cannabis for pain, 80% reported that it was very or extremely helpful, and most of those taking over-the-counter pain medications (82%) or opioid analgesics (88%) reported reducing or stopping use of those medications. Among respondents taking cannabis for sleep, 84% found it very or extremely helpful, and most of those taking over-the-counter (87%) or prescription sleep aids (83%) reported reducing or stopping use of those medications.

Conclusions: De facto medical use of cannabis for symptom relief was common among customers at an adult use dispensary, and the majority of those taking prescription or over-the-counter analgesics or sleep aids reported that cannabis use decreased their use of these medications. Adult use cannabis laws may broaden access to cannabis for the purpose of symptom relief among individuals who are unable or unwilling to register with the medical cannabis program.
**PRELIMINARY STUDY OF THE CLINICAL RESPONSE TO ORAL CANNABIS EXTRACT IN DOGS WITH REFRACTORY EPILEPSY**

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**Introduction:** In recent years, results of clinical studies have been published supporting the use of cannabis extracts for the control of convulsions, they have shown that Δ9-THC can potentiate the effects of phenytoin and phenobarbital in a generalized seizure model (Chesher et al., 1974; Chesher et al., 1975). It has been suggested that Cannabidiol (CBD) has anticonvulsant activity in both animals and humans (Karler & Turkouis, 1981; Consore & Sinder, 1986), with a high protection index, comparable to that of phenobarbital and phenytoin (Karler & Turkouis, 1981; Cunha et al., 1980). The purpose of this study was to generate a preliminary report of the findings in 9 domestic canine patients, with different types of refractory epilepsy, treated orally with an oily cannabis extract.

**Materials and methods:** We retrospectively reviewed the patients evaluated by a Veterinarian of Daya Foundation, between September 2017 and April 2018, of them we selected the 9 evaluated patients, which were medicated with a cannabis extract of artisan preparation, maintaining their usual treatment. From cannabis strains high in THC in a ratio of 20:1 of THC:CBD, the extracts were transported in an oily solvent, with application of high temperatures (≤100°C) in a proportion of 1 gr of dry matter to 10 ml of oily solvent. This extract was administered oromucosally. A dosing scheme was used according to the weight of the canines, by dose titration. Through a survey, we reviewed information on the age and breed of the pets, clinical information such as the type of convulsive syndrome/epilepsy, etiology, number of anticonvulsants previously used, characteristics of cannabis used, dose, frequency and severity of seizures.

**Results:** From the conducted surveys, the answers given by the owners of the 9 dogs of different breeds and sex were selected. The pets ranged from 1 to 11 years of age, 5 were males and 4 females. Among the etiologies were idiopathic epilepsy and seizures as a sequel to Distemper. The conventional therapies in synergistic association of drugs were levetiracetam, primidone and potassium bromide (KBr). A reduction in the frequency of seizures was recorded on average by 50%. The majority of the owners (44%) referred to having “efficient results” decreasing the frequency and severity of seizures in the satisfaction survey, 22% said they had regular results without aggravating the seizures, 11% of the owners said they had “very efficient results” and 11% of them did not continue the treatment. Among the adverse effects, an increase in appetite was reported in 22% of the patients and lethargy was registered in 11%, symptoms that diminished with time.

**Conclusions** Cannabis extract in oily vehicle, administered oromucosally, was effective in 9 canines with different types of refractory epilepsy, showing a 50% decrease in the frequency and intensity of seizures, none of these patients had cluster seizures or status epilepticus in the treatment period. The administered extract proved to be well tolerated, showing slight adverse effects that diminished with time, posing no danger for the animal.

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INTRODUCTION OF ENDOCANNABINOID SYSTEM AND CANNABIS EDUCATION WITHIN THE ITALIAN ACADEMIC AND MEDICAL SYSTEM

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Introduction: In Italy, over 12M people are suffering with chronic pain. About 3M are diagnosed with a neurodegenerative condition. If we cross these data together with the number of patients suffering from epilepsy, glaucoma, or undergoing chemotherapy, the number of Italians who could benefit from medical cannabis is estimated to reach 1/3 of the entire population: 20M people. To deal with this important need, amongst the 258,203 Medical Doctors (MDs) (i.e., specialists, GPs, and pediatricians), only approximately hundred MDs in the entire country have sufficient knowledge to be willing of prescribing medical cannabis. According to Italian laws, any MD can prescribe cannabinoids and derivatives for any health condition supported by sufficient scientific evidence, but a total lack of formal education within academia on both medical cannabis and the endocannabinoid system is preventing most patients from access to this therapy. Cannabis is distributed in Italy to patients via Galenic pharmacies, through formulation of phyto-based preparations; therefore, pharmacists as well as MDs require specific training both on medical cannabis and its pharmaceutical preparation. Currently, out of the 19,000 available pharmacies in Italy, only 600 are preparing and distributing cannabis-based medicines, a factor which contributes to the difficulties for patients to access cannabinoid-based medication.

Aim: To fill this gap we combined live academic courses and e-learning in order to increase the number of health care professionals able to deal with all the aspects related to medical cannabis.

Methods: In 2017/2018, the Department of Neuroscience of UniPD established a post-lauream (post-graduate) year-long course on the botany, medical, and legislative aspects of cannabis. The lectures are administered from a wide group of doctors and researchers from various fields and students are required to write a final dissertation. Since the academic year of 2018/2019, some of these lectures provide CME credits. Since then, Cannabiscienza, a start-up with a social vocation developed by scientists involved with either medical cannabis and/or the endocannabinoid system, has offered an integrated, localised system of scientific dissemination that combines e-learning online courses, publications, and symposiums contextualised around the possibilities and needs of Italy’s healthcare providers. The e-learning courses have received the patronage of some of the most established institutions, such as the National Council for Research (CNR) and various academies (University of Milan, University of Campania, University of Piedimont). Courses are designed to target different healthcare professionals and contain integrated quizzes, final exams, adjunct bibliography, and practical classes in a pharmaceutical Galenic laboratory.

Results: The combination of the comprehensive live course at UniPD and the highly targeted e-learning courses from Cannabiscienza have managed to attract professionals with backgrounds primarily in medicine and nursing (40% of enrolled students), pharmacists (16%), biologists (16%), humanistic studies (e.g., economists, psychologists, lawyers, and sociologists) (17%) and pharmacologists and chemists (12%). The use of distance learning is crucial in order to rapidly scale up a capillary distribution of the current scientific knowledge on the topics of medical cannabis, preparation, and the physiology of endocannabinoid system. Moreover, both these institutions are shaking the core of national communication and media coverage and thus, propelling the implementation of lectures on medical cannabis within other academies throughout Italy.

Conclusions: Combining the results of UniPD course and Cannabiscienza’s courses, a hundred more professionals are now trained on the endocannabinoid system and the plant, being able to prescribe it (MDs) and formulate compound medicines (pharmacists); UniPD has an high perceived authority within the Italian healthcare system whilst Cannabiscienza can offer education to a larger public and together these platforms combined are literally changing the state of knowledge of Italian healthcare professionals.
Using a Double Blind, Open-Label Pharmacokinetics Study to Compare the Clinical Responses of Pure Green CBD and THC/CBD Rapidly Dissolving Tablets to Blood Levels

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The incentive of creating alternative modes of cannabis administration has been increasing with the onboarding of legal states with medical and adult use cannabis programs. New products are often accompanied by claims, many of which are unsubstantiated by any scientific studies.

Pure Green Canna has conducted clinical studies and have collected subjective responses to the onset of action and efficacy of the sublingual tablets. We have now conducted pK studies to scientifically substantiate the subjective responses.

A prospective, double blind, four-treatment parallel, randomized, open-label, Phase 1 study to evaluate the pharmacokinetics (PK) of Pure Green CBD and THC/CBD tablets in healthy adult volunteers. This Statistical Analysis Plan (SAP) will describe the analyses of the PK data.

**Method: Design and Treatment.**

A total of 40 healthy volunteers will be randomized to one of four treatment arms:
- PG-001: a single dose of 20 mg CBD and 0.1 mg terpenes in a 250 mg water soluble tablet;
- PG-002: a single dose of 10 mg THC, 10 mg CBD, and 0.1 mg terpenes in a 250 mg water soluble tablet;
- PG-003: a single dose of 10 mg THC and 0.1 mg terpenes in a 250mg water soluble tablet;
- Control: an oral liquid CBD control medication.

The following analytes are the focus of this PK analysis:
- Delta 9-tetrahydrocannabinol (THC)
- 11-hydroxy-delta 9-tetrahydrocannabinol (11-OH-THC)
- 11-carboxy-delta 9-tetrahydrocannabinol (11-COOH-THC)
- Cannabidiol (CBD)
- 6-hydroxy-cannabidiol (6-OH-CBD)
- 7-hydroxy-cannabidiol (7-OH-CBD)
- 7-carboxy-cannabidiol (7-COOH-CBD)

**Results:** The analytes will be compared with the subjective effects of the rapidly dissolving THC/CBD and CBD tablets.

**Conclusions:** We conclude that the unique formulation of the Pure Green rapidly dissolving tablets does in fact have a faster onset.
Introduction: Pure Green, a USA cannabis pharmaceutical manufacturing company formulating cannabinoid-based medicines consisting of compositions of cannabinoids, terpenes, and palmitoylethanolamide in a water soluble rapidly dissolving sublingual tablet as a therapeutic treatment for many conditions for which medical cannabis is recommended.

Pure Green currently is conducting a series of clinical trials to provide data to the existing body of knowledge for the purpose of establishing efficacy, by substantiating specific cannabinoid combinations for specific indications, and for insuring patient safety. Pure Green is using a parallel path model for these studies: within the constraints of a state sanctioned legal medical cannabis program and within the constraints of the FDA. Challenges exist with both paths and we will focus specifically on the state licensed medical cannabis program.

Methods: Two separate open label studies are currently being conducted: chronic pain and menstrual pain. IRB approval obtained. HIPPA and consent documents signed. A smart phone app was designed to simplify data entry, encourage patient compliance, allow for back-end surveillance to scan for adverse effects, and permit statisticians access to the data points while being blinded to specific patients.

Results: There has been challenges at every point within the study lifecycle.

Conducting studies in legal cannabis states is not bound by the same regulations that dictate clinical trials in the FDA drug trial space. Cannabis medicine can be immediately trialed in patients without establishing safety or efficacy in animals. IRB approval is not mandatory, nor is using HIPPA compliant methods or consent signing. Even without these mandates, recruitment proved challenging. Usual methods of onboarding patients do not exist as cannabis studies cannot be advertised in newspapers, radio, or web-based platforms or in hospitals or medical universities. Doctors are reluctant to help with patient recruitment. Patients are often not compliant which leads to inaccurate or incomplete data collection. The freedom of conducting research within a state system and not the FDA is the ability to change the study. Example, the chronic pain study had to be redesigned to enhance patient compliance which lead to having to restart the study, recruit more people, and provide more medicine. However, this could not be accomplished in an FDA trial.

Conclusions: Establishing safety and efficacy of cannabinoid medicines is not required in legal states and is not yet required by the FDA as cannabis is still federally illegal. Pure Green believes that although conducting studies are difficult, time consuming, and expensive they are essential for understanding cannabinoid medicine, to prove safety and efficacy and enhance patient treatments in a defined, repeatable, and dependable way. Pure Green knows that science-based evidence is the only way to substantiate claims and differentiate treatment options for patients.
MEDICAL CANNABIS PRACTICE FOR BEGINNERS: THE FIRST EXPERIENCE OF A MEDICAL CANNABIS PRACTICE IN MEXICO CITY

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Introduction: In 2017, the Mexican General Health Law was modified, recognizing the therapeutic value of the cannabis plant and thus legalizing its use for medical and scientific purposes in the country. But the Mexican authorities have not yet provided a comprehensive set of the necessary regulations to enact such legalization, thus leaving the patients in a state of and uncertainty given the hardships that entail securing a stable, safe and accessible source of cannabis medication in an illegal, unregulated scenery such as the Mexican one, further complicated by the omnipresence of drug cartels and corruption. Furthermore, medical doctors that wish to prescribe medical cannabis to their patients are still not clear from sanctions, given that the absence of regulations and of a legal market pushes everybody to break the law, specially so since in the last couple of years there has been a widespread attention, mass and social media presence and expectations towards the cannabis plant and its medical value among the Mexican society. In this context, during the month of august 2017 a special authorization was solicited to, and issued by the COFEPRIS (Comisión Federal Para la Regulación Sanitaria) –the Mexican health regulatory authority- to open a temporary Medical Cannabis Practice in the venue of a cannabis fair, Expoweed México 2017. A team of 5 doctors provided cannabinoid medicine oriented counseling to 86 patients (we were not authorized by COFEPRIS to prescribe, so we were “recommending” medical cannabis products based upon CBD, with less than 1% THC). Product sale and exhibition at Expoweed grounds was strictly prohibited and we were under close surveillance by the regulatory authorities.

Methods and Results: 86 patients received medical cannabis counseling during two days by a team of 5 medical doctors. Patients subdivide further into 40 male and 46 female subjects, with a range of ages from 2 years old to 87 years old, with an average of 37 years of age. 13 patients had previous experience with the cannabis plant, 10 of them within a medical context and 3 of them were adult responsible users. The most common diagnosis was epilepsy (15), followed by anxiety/depression (13), cancer in different types and stages (10), lumbar chronic pain (8), diabetes mellitus/metabolic syndrome (8), autoimmune diseases (7), Parkinson’s (3), neuropathy and other types of pain (3), colitis (3), motor tics (2), dementia (1), ADD (1), glaucoma (1), autism (1). This distribution of medical diagnosis is in concordance with the most advertised uses of medical cannabis among the reports found in the internet and social media, thus indicating that the Mexican society is indeed ready for medical cannabis and its uses.

Conclusion: There is an important need to grant open access to for the Mexican population to be able to choose cannabis medicine to heal their pathologies, in a safe, certified and accessible way. The providers of health services urgently need a comprehensive, fair, transparent, sensible regulatory framework that is in accordance with the Mexican reality.
PAIN LEVEL AND MOOD EFFECTS OF SELECT TERPENES – CARYOPHYLLENE, LIMONENE, AND MYRCENE

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Although terpene effects have been discussed anecdotally, there has been very limited research on the effects of cannabis-derived terpenes on the human body. The objective of this study was to observe the before and after effects of select terpenes (specifically mood and pain levels), which in this case were caryophyllene, limonene, and myrcene.

Methods: Participants were given 3 vape pens each, with each one filled with the same THC distillate, differing in the added terpene that was spiked in. The study was a double-blind, random block design and conducted over the course of 3 weeks (one terpene vape pen per week). Each vape pen came with 2 surveys to be completed online, one to take before trying the vape pen and one after trying (taken approximately 15-20 minutes after to ensure the effects had set in). The surveys were to capture mood and pain levels before and after trying the distillate/terpene blends. The following attributes were examined: physical pain, depression, anxiety, ability to concentrate, feelings of being tired/lethargic, feelings of happiness, energy level, and hunger/appetite level. Once the dataset was complete, paired t-tests were conducted at a 95% confidence level for each before and after set of each attribute’s data to determine whether the differences were significant.

Results: While most categories showed differences, only some of them were significantly different. Caryophyllene showed to significantly increase energy and significantly decrease pain levels, depression, anxiety, and tiredness. Limonene significantly increased energy and significantly decreased pain levels. Finally, myrcene significantly increased concentration, energy, and hunger and significantly decreased pain, depression, anxiety, and tiredness.

Conclusions: We conclude from the results that the terpenes did in fact show to influence the overall mood state of the participants. They also had an influence on the pain level that the participants were experiencing by significantly lowering it. In future studies, more terpenes should be evaluated in the same fashion to see if they also have an influence on mood and pain levels as well.
SENSIBLE METHODS TO DIRECTLY AFFECT SAFETY MEASURES, RISKS AND OUTCOMES: INTEGRATEABLE APPROACH AND BALANCE AT THE MEDICAL AND SECURITY LEVEL

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In today’s dynamic view of the cannabis industry, threats grow more complex and serious each day, right beside evolving laws, research, and standard practices in today’s dynamic cannabis industry. Consequently, it is vital that an ‘integrateable’ security approach for people, process and protection is appreciated by the today’s medical professionals. To ensure that sensible methods are employed, an alliance of medical and security experts should be considered to thwart threats and directly affect risks and outcomes. Through understanding of the most fundamental theories surrounding risk control and design, strong communication and implementation of rigorous, accurate, and cost-effective security policies and practices, this alliance can reduce the evolutional costs, offer crime prediction, response planning, and improve industry surety through reduction of losses, effective safety programs, proving a greater asset in protection of business, information, and people.

Methods: Quality research in relation to cannabis-based medicine to establish safety standards of practice for non-pharmaceutical cannabis consumers, researchers and workers, while addressing regulatory, financial and cultural barriers needs to be comprehensive and calls for close collaboration. A multidiscipline approach will facilitate and expedite the necessary and ongoing safety and security needs of the industry. With D.37 Cannabis Committee, ASTM International and two decades of security expertise and a cannabis network, the objective is to demonstrate security standards developed through multi-disciplined holistic approach are better, in material and validity, authenticity, and in normative safety practices.

Results: 1) Reduce the number of loss or incidents. Decrease the potential for perceived high-risk business. 2) Safety compliance can increase approval and drive savings from third party insurance policies. 3) Improve customer service. Increase focus on customer needs. 4) Improve community good will. 5) Help reduce legal liability. Safety compliance may reduce major legal liabilities or audits. 6) Safely improve compliance, improve safety response and operations. Safety procedures may improve efficiencies and production output. 7) Drive down inefficient business costs. 8) Decrease in workplace violence incidents, intruders, and negative outcomes of anxiety or PTSD in the workplace.

Conclusions: Sensible methods are beneficial to personnel safety and compliance in the cannabis industry. On one hand, processes are standard. And on the other, people are not. Sensible methods in processes, procedures, plans and instructions are vital to protecting people and assets, and when implemented effectively, prevent theft, vandalism, and are life-saving in time of violent or serious incident. Without an ‘integrateable’ approach, knowledgeable personnel will make some decisions, but in this day and age, it is more probable to increase customer safety, staff awareness, reduce the number of staff safety insecurity, and develop an overall safety profile with a well-integrated approach versus an outsourced, usually singly to emergency responders approach.
Mounting scientific evidence supports the medicinal use of cannabis for pain, anxiety, spasticity, sleep, and other conditions that are often best served by fast-acting, traditional dosage forms such as smoking or vaping. Unfortunately, smoking and vaping expose already sick patients to chemical byproducts generated by the combustion and heating of cannabis drug substances as well as other components that are often not reported in label claims – most of which remain inadequately studied in the context of safety. Furthermore, smoking and vaping release side-stream particles that expose others to these compounds as well as nuisance odors. Sula™ is the first dry powder inhaler (DPI) that discretely delivers fast-acting, fixed doses of cannabis that are formulated with excipients having established favorable clinical safety data for pulmonary administration. Upon inhalation, Sula particles are engineered to bypass the oropharyngeal region and efficiently deposit within the lung such that, unlike smoking or vaping, essentially no particles are exhaled.

**Methods:** Sula engineered powders were prepared using a spray-drying process designed to produce micron-sized dry powders suitable for pulmonary delivery. Bulk powder was filled into size 3 HPMC capsules that are compatible with the inhaler. Multiple powder lots were assessed for THC content via HPLC.

Sula inhalation devices and THC capsules were supplied to consenting adult volunteers for the purpose of self-reporting on an investigator provided survey designed to study overall satisfaction with the DPI experience and the therapeutic effect delivered by the 1 mg dose of THC.

**Results:** 90% of survey respondents rated their DPI experience positively, with 45% responding very positive. 60% of subjects rated the effect of THC as optimal.

**Note:** HPLC data is in hand and is currently being formatted for inclusion in an updated abstract.

**Conclusions:** Sula offers patients a fast-acting dosage form that enables discrete administration of cannabis in any setting, even those where smoking and vaping are not acceptable (e.g. hospitals, restaurants, public transportation). An ongoing survey indicates that, Sula 1 mg THC dose delivers an optimal effect for most consenting adult volunteers.
Of the phenolic terpenes of hemp, Cannabis sativa, cannabidiol (CBD) has received distinguished attention recently. In fact, June 2018, the US FDA approved CBD (Epidiolex®) for the treatment of certain forms of pediatric epilepsy though the mechanism of its anticonvulsant action is not known. We have recently proposed that abundant yet poorly studied oxidative metabolites of two major phytocannabinoids, namely Δ9-tetrahydrocannabinol and CBD, could be involved in their multifaceted pharmacological activities (Ujváry & Grotenhermen, Cannabinoids 2014;9:1–8; Ujváry & Hanuš, Cannabis Cannabinoid Res. 2016;1:90–101. Based on structural similarity of certain oxidative metabolites of CBD and classical antiepileptic medicines, such as phenytoin, a similar mechanism of action for these seemingly unrelated substances has also been proposed (Ujváry & Lopata, ChemRxiv 2019. https://doi.org/10.26434/chemrxiv.7454252.v2). The presentation will provide examples of established antiepileptic drugs which target the sodium ion channel and are stereoelectronically similar to CBD metabolites. It will also survey known bidirectional interactions of CBD, usually applied at relatively large therapeutic doses, and CYP450 enzymes pointing out drug–drug interactions described so far.
South Africans are pioneers of segregation; the country leads the world in inequality, disease and violence. More than half of the country lives below the US$75 per day poverty line. South Africa ranks as the unhealthiest country in the world according to a World Health Index (WHI) based on physical and mental parameters, alcohol and tobacco use, as well as government financial support. The country is home to over seven million people living with Human Immunodeficiency Virus (HIV). The unemployment rate is around 27%. South Africa was the first country to outlaw the commercial Cannabis trade, interweaving draconian policies of social division based on skin colour, with unscientific, racist policies of drug control, pushing for international prohibition as early as the 1920s. Apartheid officially ended in 1994, but the UN “Drug Apartheid” policies are still guiding our approach to drug use today. It is estimated there are around 900,000 traditional Cannabis growers in the Pondoland region that sustain the livelihood of 3 – 4 million people. The area is also rich in Titanium; mining interests have escalated in the region to the point where some opponents are assassinated. During Apartheid, Pondoland was a shield of resistance, defying non-community led governance, leading to the Pondo Revolt, and the creation of independent unrecognised states. The Transkei and Ciskei regions of Pondoland were integrated into South Africa after Apartheid but the people weren’t uplifted and are still lacking basic services. Tourism has been proposed as an alternative to mining for job creation.

HYPOTHESIS: The aim was, to assess the feasibility to cultivate Cannabis for medical purposes in the Pondoland region of South Africa. Also, to ask two open-ended questions; what do the community need for themselves and their crops to improve quality of life?

METHODS: A site visit & meeting was held on 6th September 2018 in a hut, around a fire at Mkumbi village, a Cannabis producing village found deep in the Transkei. Consent was obtained to enter through the chief of the area. Assistance to access the village was obtained with the help of the Umzumvubu (Cannabis) Farmer’s Support Network (UFSN), which involved crossing a river on foot.

RESULTS: The Pondo people live in colourful, beehive shaped huts made from mud, without access to running water and telecommunication services. They said the South African Polices Services sprayed poison (glyphosate) on their village most recently in 2016, which caused harm to both plants and animals. Their main concern now was, not the threat of crop spraying, but having a road (and bridge) to connect with the developed world. They also wanted to be able to sell their Cannabis crops to a regular buyer at a better price of more than five US cents a gram. The Cannabis grew tall, thin stems with very small flowers, despite no irrigation, and the village was in a rain-shadow. In a study done at the University of the Free State to investigate the effects of Cannabis on MCF-7 breast cancercell growth. It was shown that Cannabis from “Pondo” was high in THCV (Tetrahydrocannabinvarin) and had the best anti-angiogenic activity in CAM assay model due to its ability to inhibit NO, MMP-1 and extracellular VEGF, compared to fifteen other cultivars from various other regions in the world and Southern Africa.

CONCLUSION: Parliament has 24 months, from the Constitutional Court judgment (September 2018) to bring legislation in line with the ruling that Cannabis is legal in one’s private space, for personal use. This threatens the Pondo farmers’ livelihoods as Cannabis is their only cash crop and the judgment sways people to cultivate Cannabis, in their own private spaces. But it also presents an opportunity to grow Cannabis tourism to invite people to possess, cultivate and consume Cannabis in Pondoland. In a Government Gazette published 23 May 2019, exemption was granted to Cannabis products containing CBD (Cannabidiol) at a daily dose of less than 20mg, and less than 0.001mg THC (Tetrahydrocannabinol), to be de-scheduled. This effectively gives an unfair advantage to foreign companies producing CBD over local Cannabis farmers in rural areas, because of the complexity to extract CBD and the strict requirements to obtain a license from the drug control authorities to cultivate Cannabis for medical purposes. It favours BigPharma because a plant can’t be patented, only a compound, like CBD. The US Government held the patent for CBD as an anti-oxidant and neuro-protectant. It expired in April 2019. The City of Cape Town announced to free up land in Atlantis, Western Cape, bringing with it an investment of US$ 40 million in Capital expenditure during the construction of phase one. The problem is the Western Cape doesn’t experience summer rainfall. In Pondoland, the climate is better suited for Cannabis cultivation, receiving year-round rainfall, being at high altitude.

Producing medical-grade Cannabis or CBD in Pondoland is not feasible in the immediate future. Legitimizing the commercial trade of whole-plant Cannabis, not just for the Pondo people, but all South Africans, presents an alternative to mining, an adjunct to tourism, an alternative to BigPharma, and an opportunity to cut a cord with Apartheid paradigms. All plants, fungi and animals have the right to life, equality, and association and should take responsibility for the effects on one another.
EFFECT OF CANNABIDIOL ON HUMAN PERIPHERAL BLOOD MONONUCLEAR CELLS AND RELEVANCE FOR IMMUNOMODULATION IN MULTIPLE SCLEROSIS

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Introduction: Cannabidiol (CBD), the main non-psychoactive component of cannabis plants (Cannabis Sativa L.), is a standard treatment for chronic pain and spasticity in multiple sclerosis (MS). However its immunomodulating potential received so far little attention. Therefore, we conducted a study to assess the effects of CBD on functional responses of human peripheral blood mononuclear cells (PBMCs), including cell proliferation and proinflammatory cytokine production.

Methods: PBMCs were isolated from buffy coats of healthy subjects by Ficoll-Paque Plus density-gradient centrifugation. Isolated PBMCs were then stimulated with anti-CD3/anti-CD28 Abs (0.1 μg/ml) and cultured alone or in the presence of CBD at 37°C under a 5% CO₂ atmosphere. Proliferation of PBMCs was measured after 120 h by flow cytometry. Supernatants and cell pellets were collected after 48 h and kept at -80°C for tumour necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) detection by real time polymerase chain reaction (RT-PCR) and enzyme-linked immunosorbent assays (ELISA).

Results: In preliminary experiments, stimulation of PBMCs with anti-CD3/anti-CD28 Abs increased TNF-α and IFN-γ mRNA levels by about 5- and 13- folds respectively. Co-incubation of stimulated PBMCs with CBD 1 µM reduced TNF-α mRNA levels down to 20.9% and IFN-ϒ down to 7.1% of stimulated levels. Treatment of PBMCs with anti-CD3/anti-CD28 increased proliferation from 0.6% to 80.3% and co-incubation with CBD 1 µM apparently showed no effect. Samples for ELISA kit assay are currently stored at -80°C and will be soon processed.

Conclusions: Results gained so far suggest that CBD may have an effect on TNF-α and IFN-γ production by PBMCs. In view of the key role of these cytokines in MS, the effect of CBD deserves additional research.
The endocannabinoid system via CB₁ cannabinoid receptors regulates neural progenitor proliferation, identity and neuronal differentiation. At early stages of corticogenesis the CB₁ receptor controls the balance of transcription factor activity Ctip2 and Satb2 that are crucial in the neurogenic program responsible of deep and upper neuronal development. Hence, CB₁ receptor ablation and THC administration in vivo interfere with subcerebral projection neuron development.

Methods: We investigated the role of endocannabinoid signalling in neuronal differentiation using mouse embryonic stem (ES) cells and human induced pluripotent stem (hiPS) cell-derived organoids subject to pharmacological and genetic manipulation of CB₁ receptors.

Results: The role of the endogenous cannabinoid signalling system in pluripotent ES neuronal differentiation was first approached by characterizing the changes in its expression along neuronal differentiation. CB₁ receptor levels, endocannabinoid metabolizing enzymes and endocannabinoid levels increased from ES cell stages to differentiated neurons, setting up a mature endocannabinoid system. Secondly, pharmacological regulation with CB₁ receptor agonists promotes ES-derived neuronal differentiation towards deep layer-like neurons at the expense of upper layer neuron development. In an opposite manner, CB₁ receptor depletion during ES-neuronal differentiation interferes with the deep versus upper layer neurogenic identity program. Finally, in order to better understand the role of CB₁ receptor signalling in human forebrain development, hiPS-derived organoids were generated in the presence of CB₁ receptor agonists. These studies confirmed the expansion of deep layer-like neuronal population and reduced upper layer-like neuronal population when.

Conclusions: These result demonstrate a cell autonomous role of CB₁ receptors and endocannabinoid signalling in neuronal development. In addition, these findings have important implications in neurodevelopmental disorders that will be discussed.
CEREBROSPINAL FLUID ENDOCANNABINOID LEVELS IN GILLES DE LA TOURETTE SYNDROME

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Introduction: Gilles de la Tourette syndrome (TS) is a complex neurodevelopmental disorder characterized by the presence of motor and vocal tics as well as psychiatric comorbidities such as attention deficit/hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD), depression, and anxiety. The underlying course of the disease is still unknown, but several lines of evidence suggest a paramount role of the dopaminergic system. Based on the clinical observation that cannabis-based medicine including cannabis and delta-9-tetrahydrocannabinol (THC, dronabinol) as well as the highly selective monoacylglycerol lipase (MGLL) inhibitor ABX-1431 may improve tics and comorbidities in patients with TS, alternatively to the “dopaminergic hypothesis” of TS an “endocannabinoid hypothesis” has been suggested.

The aim of this study was to measure cerebrospinal fluid (CSF) levels of the two most important endocannabinoids ”N”-arachidonoylethanolamine (AEA, anandamide) and 2-arachidonoylglycerol (2-AG), the endocannabinoid-like molecule palmitoyl ethanolamide (PEA), and the metabolite arachidonic acid (AA) in adult patient with TS.

Methods: We used liquid-liquid lipid extraction and simultaneous quantification by liquid chromatography multiple reaction monitoring (LC/MRM) to assess CSF levels of AEA, 2-AG, PEA, and AA in a large sample of adult patients with TS (n=20, 2 females, mean age = 36.1, ± 14.34 SD, range, 19 - 64 years, mean age at tic onset = 7.7 years ± 2.8 SD, range, 3-13 years, and mean tic severity (according to Yale Global Tic Severity Scale – Total Tic Score, YGTSS-TTS) = 23.2 ± 9.1 SD, range, 10-39) compared to controls (n=19, 13 females, mean age = 45, ± 20 SD, range, 18 - 79 years).

Results: CSF levels of AEA, 2-AG, PEA, and AA were significantly elevated in patients with TS compared to controls: AEA (mean ± SD): 2.94 ± 1.52 fmol/ml CSF (TS) vs 1.51 ± 1.08 fmol/ml CSF (controls) vs, p=0.0018; 2-AG: 0.18 ± 0.11 pmol/ml CSF (TS) vs 0.076 ± 0.04 pmol/ml CSF (controls), p=0.0003; PEA: 0.37 ± 0.38 pmol/ml CSF (TS) vs 0.14 ± 0.08 pmol/ml CSF (controls), p=0.02; AA: 40.47 ± 19.84 pmol/ml CSF (TS) vs 15.62 ± 7.49 pmol/ml CSF (controls), p<0.0001. When comparing CSF values of endocannabinoids with clinical data in patients with TS, we found no influence of patients’ sex, age, medication and tic severity. However, levels of 2-AG correlated with the severity of ADHD (p <0.01).

Conclusions: This is the first study, demonstrating a direct involvement of the endocannabinoid system (ECS) in the pathophysiology of TS. It can be speculated that alterations in the ECS either represent secondary changes in order to compensate for alterations in other neurotransmitter systems such as the dopaminergic system or, alternatively, represent the primary cause of TS.
AUTOIMMUNE ENCEPHALITIS TREATED WITH CANNABIS CASE REPORT

Dr Max Alzamora (Perú)

**Introduction:** The term encephalitis makes reference to a conjunction of inflammatory disorders of the brain of diverse etiology and with a complex differential diagnostic. The clinical manifestations are multiple including cognitive alterations of the behavior, conscience level reductions, focal deficits, convulsive crisis and dementia. In centers interested in encephalitic epidemiology approximately 65% of patients ultimately finish without a definitive diagnostic. The implication of these discoveries are very important, mortality and irreversible deficit frequencies are elevated in patients with encephalitis.

**Method and Results:** 15 year old female patient without any medical pathology history or priors, suddenly acquires the disease with fibril syndrome and post convulsive syndrome, deterioration in higher mental functions and V grade impairment with limited total functions. She was hospitalized for 3 months time, in which the convulsions persisted and increased (5 times a day) even though she was receiving anticonvulsive treatment. Tomographic images showed signs of encephalitis. All of the auxiliary laboratory exams concluded negative including cerebrospinal fluid (NMDA -, virus herpes). Treatment for viral encephalitis was done for 21 days without any signs of improvements. Coma induction for 45 days in the intensive care unit with intubation and artificial ventilation, during this time she presented inpatient pneumonia and pharmacological hepatitis. After which she passed to the intermediate care unit, the convulsive crisis reduced in frequency but not in intensity. She cannot control sphincters, impossibility to sit, and being fed through a nasogastric tube. She is released 5 months later in a wheel chair, with nasogastric tube. Disconnected from her environment and being treated at home with Midazolam Clobazam, Phenobarbital. One year later she began treatment with biological pharmaceuticals (Rituximab) and immunoglobulin, during this time functions improved but there was no improvement to the convulsive crisis to which she had developed anxiety symptoms and euphoria.

Finally one year later she began a cannabis based treatment, with Charlotte Web Oil 1000mg of hemp oil 1000 mg of hemp oil 1mL every 8 hours, reducing the frequency of convulsions to 12 convulsions per week. Motor skills improved and finally she achieved walking without any difficulty, it also reduced aggressiveness and anxiety. However insomnia persisted. 10 months later she began treatment with RSHO Oil 1000 mg of hemp oil 1mL every 8 hours, reducing frequency of convulsions to 5 times per week, and improving motor skills. 7 months after beginning treatment with artisanal Harle Tsu strain (500 mg of cbd + 50 mg of Thc – full spectrum) 0.5 mL every 8 hours with which she achieved reducing convulsions to 3 times per month, she responds when being called and improved insomnia, anxiety, euphoria and now recognizes her family members.

**Discussion and Conclusions:**

- Patient with encephalitis and convulsive syndrome who did not respond to pharmaceutical treatment presented torpid evolution, but with cannabis based treatment presented favorable evolution.
- Evidences differencing in neurologic response with distinct cannabis strains.
- With cannabis based treatment, we witnessed intensity improvements and frequency reduction of convulsive crisis, functionality improvements, connection with her environment, and improvement in higher mental functions.
Introduction: Medicinal cannabis is frequently used by patients for various indications. Cannabis oils not always taste nicely and smoking or vaporizing cannabis is unhealthy and not preferred by most patients. Current available products often contain different amounts of cannabinoids, have a slow and variable absorption, inconsistent quality, and are difficult to dose accurately. Therefore, we have developed a tablet formulation (named Namisol®) that is patient friendly, safe and provides accurate administration of pure, natural Δ9-Tetrahydrocannabinol (THC).

Methods: Pharmacokinetics (PK) of Namisol® were analysed in healthy volunteers (HV), elderly, and Chronic Pancreatitis (CP) patients. Plasma concentrations of THC, 11OH-THC and THC-COOH were determined using a validated LC-MS/MS method according to GLP. PK parameters were calculated using non-compartmental and compartmental analysis. Dose-proportionality was assessed for Cmax and AUC(0,∞).

Results: PK data showed that the onset of action after a single dose of Namisol® ingestion is usually within one hour, with peak plasma concentration within 1 hour (tmax 0.65-0.93 h. in HV). The half-life can vary from 1.2 to 1.32 hours for a single dose, whereas multiple dosing resulted in a half-life of approximately 3.2 hours. Elderly subjects showed a comparable PK profile but with a slightly larger inter-individual variation compared to young adults. The tmax is longer in CP patients (tmax 1.43-2.05 h.) than in HV. Cmax and AUC(0,∞) were dose proportional and tmax and t½ were similar for all doses in HV. The results show an extensive first-pass effect due to hepatic metabolism of THC to different metabolites such as 11-OH-THC and THC-COOH.

Conclusions: These results show that THC from Namisol® tablets is rapidly absorbed and has a dose-linear PK-profile. In CP patients THC was absorbed somewhat slower than in healthy subjects, which can be related to malabsorption in these patients. However, it can also be related to the fed condition of these patients during Namisol® intake. The tmax of THC plasma concentrations was shorter, Cmax higher, and variability was smaller for Namisol® than reported for oral dronabinol. A fast onset of action and a less variable response are expected to lead to a more rapid and consistent clinical response, whereas the higher Cmax may indicate a possibly larger clinical effect.
Of the phenolic terpenes of hemp, *Cannabis sativa*, cannabidiol (CBD) has been receiving distinguished attention. CBD was approved in 2018 by FDA in the USA (Epidiolex®) and, in 2019, by EMA in the European Union (Epydiolex®) for the treatment of certain forms of pediatric epilepsy. The mechanism of anticonvulsant action of CBD, usually applied at relatively large therapeutic doses, is not known. It has recently been proposed that abundant yet poorly studied oxidative metabolites of Δ⁹-tetrahydrocannabinol and CBD could be involved in the polypharmacology of these major phytocannabinoids (*Ujváry & Grotenhermen, Cannabinoids 2014;9:1–8; Ujváry & Hanuš, Cannabis Cannabinoid Res. 2016;1:90–101*). Based on stereo electronic similarity of primary oxidative metabolites of CBD and classical antiepileptics, such as phenytoin, a similar mechanism of action for these seemingly unrelated substances has also been proposed (*Ujváry & Lopata, ChemRxiv 2019. https://doi.org/10.26434/chemrxiv.7454252.v2*). The presentation provides further examples of established antiepileptic drugs which target the sodium ion channel and which are stereoelectronically similar to CBD metabolites, and surveys known and potential drug–drug interactions of CBD. Focus will be on CYP450 isoenzymes affected by CDB or involved in the formation of bioactive CBD metabolites. It is also suggested that metabolites of CBD might serve as structural leads to new antiepileptic medicines.
Introduction: A known fact in the formal healthcare sector, which is holding back the fully acceptance of medical cannabis, is the lack of clinical trial data. A further fact that we resulted in by extensive literature research, is that there are more than 100 million patients in unmet needs in the European Union. According to case studies and other forms of uncontrolled studies, these patients could potentially benefit from cannabis treatments.

Methods: Because of the extensive and complexity of the systematic review and meta-analysis to identify the number of patients in unmet needs in 9 conditions in the European Union, we consider our research as ongoing, but we are hereby presenting our first findings.

Results per condition followed by the number of patients in unmet need in the European Union:

- Chronic pain: 59441000.
- Epilepsy: 2972040.
- Pain in arthritis: 36803050.
- Pain in cancer: 502320.
- Chemotherapy induced nausea and vomiting: 1107600.
- Rheumatic diseases: 31206525.
- ADHD: 15308303.
- Fibromyalgia: 13002710.
- Therapy-resistant glaucoma: 24519420.

Conclusions: Given the fact that the number of patients in unmet needs in Europe is alarming, patients should have the right to access medicinal cannabis standardized products through the formal health care sector.
COLOMBIAN PHYSICIANS’ PERCEPTIONS, EXPERIENCES AND KNOWLEDGE AROUND MEDICAL CANNABIS USE: A PILOT SURVEY STUDY

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Background: Colombia’s medical cannabis legislation was enacted in 2016, and while physicians will be the professionals in charge of prescribing cannabinoid-based medicines, no systematic effort has been made to understand their attitudes and knowledge regarding medical cannabis.

Methods: An anonymous, online 32 item- survey tool assessing the level of knowledge, attitudes and experience physicians have regarding medical cannabis was developed and administered to physicians who are part of Clínica Las Américas, a tertiary care institution located in Medellín, Colombia, South America.

Results: 80 physicians completed the 32 item-survey (40% response rate). 84% of participants thought that medical cannabis may be of benefit in the treatment of patients with chronic and debilitating illnesses. 20% of participants thought that using medical cannabis represented serious risks to physical health, and 21.9% believed that using medical cannabis represented a serious risk to mental health. Consistent with similar surveys and the medical evidence, the most commonly cited conditions for which physicians would prescribe medical cannabis were chronic pain that does not respond to pharmaceuticals, cancer-related symptoms, fibromyalgia, spasticity disorders and epilepsy. The most common obstacles to prescribe medical cannabis, as identified by the survey responders, were lack of prescription guidelines, lack of knowledge around the appropriate use of medical cannabis, concern that patients may be seeking cannabis for recreational purposes. Although access to legal medical cannabis products at the time of the survey were available, 19% of respondents reported having already recommended cannabis for medical purposes to their patients. 88% or participants reported “low” knowledge on dosing and creating treatment plans, 68.2% related “low” knowledge levels on precautions and ability to identify medical cannabis misuse signs. 90.6% of survey respondents believed that medical cannabis education should be included in the curriculum of the different medical specialties

Conclusions: This is the first systematic attempt made in Latin America to understand the level of knowledge, experience and perceptions potential prescribers have with respect to medical cannabis. Consistent with similar studies, results from this research show there is a discrepancy between attitudes and the knowledge base regarding medical cannabis. This pilot study identified medical education gap areas and barriers for the wider implementation of cannabis as medicine.
INVolvement of CB2 cannabinoid receptor in the reinforcing effects of chocolate flavoured-pellets and eating addictive-like behaviour

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This study was aimed to evaluate the involvement of CB2 cannabinoid receptor (CB2R) in the reinforcing effects and eating addictive-like behaviour promoted by chocolate-flavoured pellets. We used a recently validated operant model of eating addictive-like behaviour in mice deficient or overexpressing CB2R and wild-type littermates (WT).

Methods: Three hallmarks of addiction were evaluated at two different time points during the early and late training period in this model: persistence of food seeking during a period of non-availability of food, motivation for food and perseverance of responding when the reward was associated with a punishment. Each mouse was classified as resistant (0 criteria) or vulnerable (2-3 criteria) to this addictive-like behaviour considering these hallmark criteria.

Results: Our results revealed a significant difference in the percentage of mice reaching 0 criteria when compared CB2R deficient mice (0%) with control mice (60%) during the early period, although no major differences were reported between mice overexpressing the CB2 protein (33.3%) and control mice. During the late period, a reduced but not significant percentage of CB2R knockout mice resistant to addiction was shown, suggesting that CB2R seems involved in the predisposition to addiction.

Conclusions: CB2R may constitute an interesting potential mechanism involved in eating addictive-like behaviours.
TARGETING CB2 CANNABINOID RECEPTORS TO SUPPRESS ANTIRETROVIRAL-INDUCED NEUROPATHIC PAIN

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Painful peripheral neuropathy is the most common neurological complication associated with human immune deficiency virus (HIV) infection, affecting approximately one third of people living with HIV. HIV-associated peripheral neuropathy is also induced by antiretroviral drugs such as 2’-3’-dideoxycytidine (ddC). Antiretroviral-induced neuropathic pain remains a major source of morbidity and a detriment to quality of life of patients living with HIV/AIDS. Thus, there is a need for safe and effective pharmacotherapies for pain that lack unwanted side effects (i.e. psychoactivity, abuse liability).

Methods: We developed a mouse model of anti-retroviral-induced neuropathy produced by ddC treatment. We asked whether cannabinoid CB2 agonists would suppress anti-retroviral-induced neuropathic pain and identified cell types underlying CB2-mediated antinociceptive efficacy using a conditional deletion approach. We used a transgenic mouse (CB2fl/fl) in which enhanced green fluorescent protein is under control of the CB2 promoter (Lopez et al. (2018) J. Neuroinflammation 15: 158) to aid in detection of CB2 receptors in different cell types. In this mouse line, the CB2 gene is flanked by loxP sites allowing for conditional deletion of CB2 receptors from cells expressing Cre recombinase. We examined the impact of conditionally deleting CB2 from either peripheral sensory neurons (by generating advillinCre/++;CB2fl/fl mice) or excitatory neurons (by generating NEXCre/++;CB2fl/fl mice) on both ddC-induced neuropathic pain as well as CB2 agonist efficacy.

Results: Mice treated with ddC developed robust hypersensitivity to both mechanical and cold stimulation. Multiple CB2 agonists, AM1710 and LY2828360, suppressed ddC-induced neuropathic pain in wildtype mice but not in global CB2 knockout mice. AM1710 and LY2828360 suppressed ddC-induced neuropathic pain in CB2fl/fl mice, but not in advillinCre/++;CB2fl/fl mice. The effects of conditional deletion of CB2 receptors from primary sensory neurons were also mimicked in NEXCre/++;CB2fl/fl mice. Moreover, in separate studies, the CB2 agonist LY2828360 suppressed ddC-induced neuropathic pain in CB2fl/fl mice rendered tolerant to morphine, an opioid analgesic, and also reversed established morphine tolerance. Both effects were absent in advillinCre/++;CB2fl/fl mice.

Conclusions: The present studies provide the first evidence that CB2 receptor activation may alleviate HIV-associated neuropathic pain in a mouse model. Removal of CB2 receptors from peripheral sensory neurons or excitatory neurons eliminated the antinociceptive efficacy of CB2 agonists. CB2 agonists reduce neuropathic pain induced by diverse toxic challenges without producing tolerance. Moreover, CB2 agonist treatment suppressed the development and reversed established tolerance to opioids. Our studies support previous preclinical and clinical research suggesting that the cannabinoid system may be targeted to efficaciously alleviate HIV-associated sensory neuropathy.

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CANNABINOID TYPE 2 RECEPTORS MEDIATE A CELL TYPE-SPECIFIC SELF-INHIBITION IN CORTICAL NEURONS

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Endogenous cannabinoids are diffusible lipid ligands of the main cannabinoid receptors type 1 and 2 (CB1R and CB2R). In the central nervous system endocannabinoids are produced in an activity-dependent manner and have been identified as retrograde modulators of synaptic transmission. Additionally, some neurons display a cell-autonomous slow self-inhibition (SSI) mediated by endocannabinoids. In these neurons, repetitive action potential firing triggers the production of endocannabinoids, which induce a long-lasting hyperpolarization of the membrane potential, rendering the cells less excitable. Different endocannabinoid receptors and effector mechanisms have been described underlying SSI in different cell types and brain areas.

Methods: By using patch clamp recordings combined with pharmacological methods and genetic deletion models we investigate SSI in different cell types of layer 2/3 in the somatosensory cortex: in pyramidal cells (PC), in regular spiking non-pyramidal cells (RSNPC) and in fast-spiking interneurons (FS). In addition, we investigate the underlying mechanism by which SSI is implemented.

Results: High frequency burst of action potentials induced SSI in PC and RSNPC, but not in FS. The hyperpolarization was accompanied by a change in input resistance due to the activation of G protein-coupled inward-rectifying K⁺ (GIRK) channels. A CB1R-specific agonist induced the long-lasting hyperpolarization, whereas preincubation with a CB2R-specific inverse agonist suppressed SSI. Additionally, using cannabinoid receptor knockout mice, we found that SSI was still intact in CB1R-deficient but abolished in CB2R-deficient mice.

Conclusion: Taken together, we describe an additional SSI mechanism in which the activity-induced release of endocannabinoids activates GIRK channels via CB2Rs. These findings expand our knowledge about cell type-specific differential neuronal cannabinoid receptor signaling and suggest CB2R-selective compounds as potential therapeutic approaches.
PERCEIVED EFFICACY OF MEDICAL CANNABIS FOR TREATMENT OF ANXIETY SYMPTOMS AMONG PERSONS WITH POST-TRAUMATIC STRESS DISORDER (PTSD)

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Introduction: Anxiety and chronic pain co-occur frequently with post-traumatic stress disorder (PTSD) as a result of past trauma. Medical cannabis (MC) users have been shown to reduce or discontinue opioid-based pain medications and anti-anxiety medications due to improved symptom management and decreased risk of medication side effects. Despite PTSD being one of the most commonly reported conditions for persons qualifying for use of MC across states in the U.S., patterns of discontinuation or reduction of prescription medication with MC use among persons living with PTSD are largely unknown.

Methods: We conducted a cross-sectional online survey of persons with a state medical cannabis card in Illinois recruited from licensed MC dispensaries across the state, and analyzed data from a subsample of persons qualifying for MC based on a PTSD diagnosis (N=81). We summarized participant characteristics and grouped participants by their use of benzodiazepines and opioids (maintenance, reduced use, discontinuation) to treat anxiety and pain, respectively. Analysis of variance between groups was conducted to assess mean differences in anxiety symptoms, frequency of MC use, and perceived efficacy of MC to treat anxiety and pain.

Results: Most common symptoms treated with MC included anxiety (79%), depression (68%), severe pain (58%) and insomnia (58%). Almost one-half of the sample reported smoked flower as preferred ingestion method, and an additional 31% reported using combination of ingestion methods. Mean differences in perceived efficacy of MC to treat anxiety varied significantly among persons who discontinued benzodiazepine use (M=3.86, SD=.35), reduced benzodiazepine use (M=3.73, SD=.47), and maintained benzodiazepine use (M=3.37, SD=.76). Mean anxiety symptoms and frequency of MC use did not vary significantly among the benzodiazepine groups. Perceived efficacy of MC to treat pain and frequency of MC use did not vary significantly by corresponding opioid use groups.

Conclusion: Findings from this exploratory analysis of anxiety, chronic pain and MC use among persons living with PTSD suggest that MC is perceived as an efficacious substitute for benzodiazepines. Longitudinal research is needed to disentangle potential efficacy of MC and patient-centered outcomes for treatment of co-morbid symptoms associated with PTSD.
The use of Cannabis-based preparations to complement the treatment of diseases such as refractory epilepsy, Parkinson’s, Cancer, Fibromyalgia and Chronic pain has currently increased in Argentina. Many of these are homemade preparations that are made using different varieties of Cannabis sp. and several extraction methods; which generates great variability in their composition. Therefore it is necessary to standardize crops and production processes of cannabis byproducts. We have worked with three varieties of Cannabis sp. denominated Therapeutic Argentine Strains (CAT 1, 2 and 3) maintained under culture conditions in the CIM laboratory. Cannabinoid profile determination was carried out on samples of seeds, roots, leaves, flowers and stem of CAT 3. The cannabinoid profile on CAT 1 flowers was determined before and after heat treatment. Similarly, the cannabinoid profile was analyzed in samples of alcoholic extract, resin and oil obtained from CAT 2 flowers, which are used in basic science studies.

Methods: The Therapeutic Argentine Strains (CAT 1, 2 and 3) were cultivated under the following conditions: vegetative growth chamber (22 °C, humidity: 45%, light/dark cycle: 18/6 hours, mercury lamps: 530 µmol/m². sg); Flowering chamber (25 °C, humidity: 60%, light/dark cycle: 12/12 hs, Sodium lamps: 1007 µmol/m².sg). CAT 1 flowers subjected to heat treatment were placed in an oven at 145°C during 7 min. The procedure used for cannabis oil production consisted of an alcoholic extraction of CAT 2 flowers, followed by low temperature evaporation (rotary evaporator BUCHI) to obtain the resin and subsequent dilution in the edible oil. Cannabis tissue samples were extracted with ethanol and, after a clean-up process, the cannabinoid profile was analyzed by HPLC-UV/DAD using analytical standards to identify and quantify (Cerilliant).

Results: THC-A and CBD-A were found in all plant tissues studied, while CBN was not observed in any tissue. Flowers and leaves, the two richest tissues in cannabinoids, presented a different THC/CBD ratio (Flowers: 23:1, Leaves: 3.5:1). The heat treatment of flowers produced a quantitative decarboxylation of the acidic cannabinoids in THC and CBD respectively, without degradation due to the absence of CBN. The analysis of alcoholic extract, resin and oil indicated the existence of small losses of cannabinoids (17% and 12%) between the different stages; however the THC/CBD ratio (22:1) was maintained in all the products analyzed.

Conclusions: We conclude from these findings, that the leaves are an adequate source to produce extracts with different THC/CBD ratio with respect to flowers of the same variety; and it is necessary to advance in these studies in order to optimize processes and adjust variables such as the tissue and the variety used in the extraction, the temperature and time used to obtain the best cost/benefit ratio in terms of the THC/CBD ratio required. These studies will make a contribution of necessary data for the dosage and the reduction of damages.
EXPERIENCE IN THE USE OF CANNABIS ON PATIENTS FROM THE DEPARTMENT OF PALLIATIVE CARE OF THE ANGEL ROFFO HOSPITAL FOR ONCOLOGIC CARE.

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Thanks to therapeutic users and civil organizations, in March of 2017, in Argentina, it was possible to pass Law 27,350 for the medicinal use of cannabis, which allows for research into medicinal cannabis and regulates the access to medicinal cannabis. However, as of date, only a handful of patients managed to access the medicinal cannabis. This situation forces mother and patient organizations to grow and process cannabis plants, in order to improve the health and life quality of kids, patients and their families. The risks this kind of practices entail are many, and we can frequently see police raids and the seizure of the plants in the growers’ homes, and the growers are often prosecuted and even sentenced to 4 to 15 years in prison. Such situation has allowed for the growth of an illegal market of cannabis oil with no control whatsoever. However, it is getting more and more frequent to see patients that choose to use medicinal cannabis and ask their doctors to assist them in the process. This is mostly seen in oncologic patients who receive palliative care and who are treated at the Department of Palliative Care of the Hospital Angel Roffo for Oncologic Care (University of Buenos Aires). They use homemade oils or they buy them in the black market; we don’t have any information on the cannabinoids that are present in these oils and in which proportion. We want to stress that it is mandatory to know the concentration of the cannabinoids found in the different presentations used for medicinal purposes in order to be certain of the dosage.

The aim of this work is to study the cannabinoids that are present in the oils used by the patients who are treated at the Unit of Palliative Care of the Hospital Angel Roffo and to check on the evolution of the patients.

Methods: Cannabis oil samples were extracted with ethanol and, after a clean-up process, the cannabinoid profile was analyzed by HPLC-UV/DAD using analytical standards to identify and quantify (Cerilliant). During 2017 and 2018, 150 patients received treatment. 64 of said patients had medical charts at the Roffo Institute (IOAR) (43%) and 86 of them are patients who looked for a second opinion, and who have not had a follow-up at the hospital. Out of the 64 patient at the Institute, 33 of them have an observational record with posterior follow-ups. From these patients, we could collect data regarding the reasons why they started using these oils, adverse effects, influence in their workplace and social life, and subjective improvement of pain and relationship to the use of opioids.

Results: The first results indicate that, over 159 samples of cannabis oil, with an average of 7.04 mg/ml and a standard deviation of 17.4 mg/ml, 21% of the patients show a 25% to 60% decrease of the DEMO, with the use of cannabis derivates, while the 60% said that they felt an improvement in their social life and in their family environment.

Conclusions: It is necessary to enforce Law 27350 of medicinal cannabis so that everyone can have access to good quality cannabis, subject to proper controls.

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CANNABIS IN MEDICAL SERVICE: FIRST EVALUATION OF PATIENTS RECEIVING ADJUVANT TREATMENT WITH CANNABIS OIL IN ARGENTINA.

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In Argentina, the use of cannabis-based products as adjuvant treatment of different pathologies has recently increased. The Argentine legislation only contemplates the treatment of refractory epilepsy. However, the population is using these products more widely. In this scenario, doctors face the situation of providing treatment and support to patients who frequently use homemade cannabis-based preparations. Therefore, the objective of this work was to follow up 60 patients treated with cannabis oil obtained from a cannabis strain with CBD/THC ratio 2:1. This report results from the work of a physician, who provides the treatment to patients, embedded in an NGO that provides the cannabis oil; and a research group that chemically characterizes them.

Methods: The updated medical records of 60 patients with various pathologies, treated orally with cannabis oil obtained from the strain studied, were analyzed. The characterization of cannabinoid profile of the strain employed was performed by HPLC/UV-DAD obtaining a CBD:THC ratio 1.5:1, where 66% of total CBD is found as CBD-A and 45% of total THC as THC-A.

Results: 1) The gender of the patients was 63% female and 37% male presenting the following age distribution: children (0-15 years) 13%, youth (16 to 25 years) 4%, adults (26 to 60 years) 35%, mature (61 to 80 years) 35% and long-lived (over 81 years) 13%. 30% of patients had neurological disorders (predominantly epilepsy or Parkinson’s disease), 43% had chronic pain (mainly due to cancer, discopathy, osteoarthritis or bone disease), 13% had psychiatric disorders (ADHD, PDD) and 14% had multiple pathologies. 2) 73% of patients showed improvement in the symptoms and only 13% reported adverse effects (lethargy, nausea, hypotension, dizziness or increased appetite) that revert by adjusting the dose of cannabis oil and traditional medication. 3) 31% of patients decreased the doses of medications received, registering a dose reduction of 65 ± 29% for opioids, 80 ± 29% for benzodiazepines, 70 ± 24% for NSAIDs and 75 ± 25% for anticonvulsants. 4) The effective dose of total cannabinoids employed in these treatments was 0.6 ± 0.3 mg/day; being 1.4 mg/day and 0.1 mg/day the highest and lowest dose used respectively.

Conclusions: Our results indicate that, in the population studied, the beneficial effects of cannabis oil treatment were more important than the adverse effects, which can be reversed by adjusting the doses. Likewise, has shown significant dose reductions in medications such as opioids, benzodiazepines, NSAIDs and anticonvulsants, resulting in a benefit in patients under polypharmacy. Therefore, it is important to generate a protocol that allows register patients treated with cannabis-based products and their evolution during treatment in daily medical practice. This information could integrate a database to assess the scope of medical cannabis in larger populations.
SYMPTOM PROFILE OF BREAST CANCER PATIENTS SEEKING MEDICAL CANNABIS IN PENNSYLVANIA’S NEW MEDICAL MARIJUANA PROGRAM

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Introduction: Pennsylvania launched its Medical Marijuana Program (PA MMP) in 2018 for patients with 17 serious medical conditions, including cancer. Certified-physician qualification of patients followed by an independent evaluation by a trained HCP at a medical marijuana dispensary, are both required.

Methods: A history and physical, including a full review of systems was performed on each patient. The diagnosis of cancer was verified. The Prescription Monitoring Program database was checked for opioid use; and all medications were assessed for drug-drug-interactions. Consent was obtained, certification was performed; the dispensary was chosen by the patient.

Results: Of the 54 cancer patients certified in the first 10 months of the PA MMP in a community academic hospital, 31 had breast cancer: 22 had early stage and 9 had metastatic disease. Median age was 64, with a range of 26 - 86.

Of the 22 women with non-metastatic disease, 16 (73%) sought cannabis for pain, of whom 4 (25%) had chemotherapy-induced peripheral neuropathy (CIPN) and 3 (19%) had exacerbation of a pre-existing chronic pain condition. Eleven (50%) had insomnia and 10 (45%) had anxiety—of whom 8 had both symptoms. One of 22 reported nausea. Three recreational users wanted to shift over to medical grade quality products. Of the 9 patients with metastatic breast cancer, 8 (89%) had pain and 8 (89%) reported anxiety. 33% had insomnia (3/9), anorexia (3/9), and nausea (3/9). Each patient reported an average of 3 symptoms. About half of patients with pain expressed fear of opioids and were highly motivated to avoid, stop, or reduce its use. Causes of pain included cancer, CIPN, worsening of a pre-existing pain syndrome, or muscle/joint pain from hormonal therapy. All patients were seeking a medical solution for significant symptoms; only 2 also admitted a desire to get high. CBD dominant sublingual preparations were primarily recommended. Topical products applied to painful areas, were also commonly utilized (CBD or THC dominant, or 1:1 preparations). Except for immediate relief of acute pain, smoking and vaping were strongly discouraged to avoid any toxicity to the lungs, especially during radiation and chemotherapy. The physician-facing patient certification database, however, does not interface with the dispensaries’ seed-to-sale database. Therefore, we are unable to know which products—type, dose, source, method of delivery—were actually purchased by each patient.

Conclusion: Women with early stage and metastatic disease sought medical cannabis for management of pain (73-89%, resp), anxiety (45-89%), insomnia (50-33%), nausea (4% and 33%), and anorexia (0 and 33%). Most patients suffered an average of 3 symptoms. Pain was rarely experienced alone; insomnia and anxiety were frequently combined. Other benefits of medical cannabis included the utilization of safer products and safer methods of delivery. Fear of opioids motivated many patients to avoid, reduce or stop opioids. For optimal continuity of care, the physician and dispensaries databases must be integrated.
Effects of Medical Cannabis on Health-Related Quality of Life: An Open-Label Observational Cohort Study

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Introduction: Patient access to medical cannabis is still limited given safety concerns, current lack of consensus, and high-quality evidence regarding its efficacy among treating physicians. Particularly, the impact on patient-reported outcomes, such as health-related quality of life (HRQoL), remains inconclusive. Our objective was to evaluate the extent to which medical cannabis consumption affects different HRQoL domains over a one-year period.

Methods: From Nov-2015 to Apr-2019, patients attending Specialized Medical Cannabis Clinics (SMCCs) and approved for medical cannabis treatment, were recruited by physicians to participate in an open-label, observational cohort study. HRQoL of patients who signed informed consent was assessed using the Short-Form 36 at baseline (with a physician in attendance), and at monthly intervals (online), up to one year. Demographics, medical diagnosis, symptom severity, treatment regimen and cannabis experience were recorded. Adverse events were coded in MedDRA system organ SOC classes. Descriptive and inferential statistics were applied on two separate patient cohorts, defined by the primary reporting symptom for which medical cannabis was used: Anxiety or Pain, and composed of patients who completed the baseline (Tₜₒᵢ₇), mid-treatment (Tₘᵢ₇, 6-months), and post-treatment (T₉ₒᵢ₇, 12-months) evaluations.

Results: Of the 769 patients approved for treatment across 10 SMCCs, 116 had complete follow-up data and were included in the analysis. Patients were mainly experienced cannabis users (70%). Primary diagnoses included Chronic pain (22%), Fibromyalgia (7%), Anxiety (5%), Depression (5%), and 41.5% reported additional secondary conditions. Cannabis administration method varied: vaping (44%), smoking (36%), oil (17%), and edible (3%). Patients were further stratified by their primary symptom of treatment, Anxiety [AC] (n=60), and Pain [PC] (n=56). Patients in AC vs. PC were similar in sex composition (55.4% Male vs 58.3% Male, respectively), and mean age (39 ±11 vs 45 ±12, respectively). For the key outcomes, improvements were noted from Tₜₒᵢ₇ - Tₘᵢ₇ in some components of HRQoL: AC - Bodily pain (mean ± SD: 40.0±10.5 to 42.2±10.4; p=0.041), Vitality (36.4±11.3 to 38.9±12.0; p=0.06); and PC – Vitality (35.1±10.9 to 41.8±4.4; p<0.001). From Tₜₒᵢ₇ - T₉ₒᵢ₇, significant improvements were detected: AC – Vitality (36.4±11.3 to 38.9±11.9; p=0.014); PC – Bodily pain (31.2±8.0 to 34.0±9.8; p=0.016). Notably, no significant deteriorations were observed in any of the HRQoL domains. Only 6 non-serious adverse events were reported: Psychiatric disorder (n=3), Gastrointestinal disorder (n=2), and Vasular (n=1).

Conclusion: One-year medical cannabis use was found to be beneficial in improving certain HRQoL domains. Patients with Anxiety vs. Pain as their primary symptom, demonstrated significant gains in Vitality (Mental) vs Bodily pain (Physical) domains, respectively. Although the study has limitations (e.g. lack of control group), it provides important real-world evidence of the effectiveness of cannabis in medical practice and encourages the examination of such patient-reported outcomes in larger, better controlled study populations.
REAL WORLD EVIDENCE ON SPECTRUM THERAPEUTICS PATIENT USERS, PRODUCTS, AND SYMPTOMS

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Introduction: Medical cannabis use has largely been a patient-driven phenomenon, and over the years, there has been an increase in scientific evidence demonstrating that cannabis medicine is associated with therapeutic efficacy across numerous therapeutic indications. In May 2019, Spectrum Therapeutics launched a range of products with varying (THC:CBD) ratio content; RED (17-20:<1), BLUE (8-11:8-11), YELLOW (<1:20), and ORANGE (12-15: <1) for the Canadian cannabis program. Our study aims to describe the Spectrum patient cohort and assess the association between product used and symptomatology.

Methods: We used archival data captured by Strainprint, a free App (HIPPA, PIPEDA, and PHIPA compliant), designed for patients treating with cannabis. The following variables were collected: basic demographics, medical conditions, treated symptoms, product name, administration method, and number of sessions (session=each time a patient logs into the App and inputs data. A patient can enter up to 3 symptoms in one session). A descriptive analysis of individuals using Spectrum products was undertaken.

Results: Data from 629 Spectrum product users who collectively entered 27 036 sessions was analyzed. Mean age 36.3 ±10.8 years (range 18 to 74 years), and 58.7% identified as female. The majority of users resided in Canada (97.1%), largest proportion from Ontario and Alberta (33.7%, 26.4%, respectively). The median number of medical conditions identified per individual was 4, with Anxiety disorder, Back pain and Chronic pain as the most frequent. A total of 66 symptoms were treated over the 27 036 sessions, and the most common treated symptoms included: Muscle Pain (10.7%), Anxiety (10.1%), Joint pain (9.2%), Insomnia (7.4%), and Joint stiffness (6.8%). The top 3 products in descending order consumed for these symptoms were Muscle Pain (RED 31.8%, BLUE 23.5%, YELLOW 18.4%), Anxiety (YELLOW 40.8%, RED 21.2%, BLUE 15.6%), Joint Pain (RED 34.3%, BLUE 23.7%, YELLOW 23%), Insomnia (RED 67.4%, BLUE 12.1%, ORANGE 10.2%). Upon further stratification, significant differences were observed between sex and the product profile consumed. Oil was more prominent among females vs males (53.8% vs 30.2%, respectively; p=0.001), and vaping among males vs females (39.9% vs 25.7%, respectively; p=0.001). Higher consumption of BLUE product was observed in males vs females (22% vs 17.5%, respectively; p=0.022), and higher YELLOW consumption in females vs males (29.4% vs 19%, respectively; p=0.022). Product used also varied between age tertiles (<31 vs 31-39 vs >40) significant differences were reported for: BLUE (10.1% vs 12.7% vs 30.8%; p=0.001), RED (27.7% vs 40.4% vs 29.4%; p=0.001), and YELLOW (32.5% vs 24.4% vs 18.7%; p=0.001).

Conclusions: Our results demonstrate that higher THC content products were consumed for treating symptoms of pain and sleep, and higher CBD content products for anxiety. However, there seems to be variations in patient preference by age and sex, which could impact treatment outcomes. Although this data is limited by lack of control group(s) and blinding, it generates important hypotheses for future research. A follow up analysis on perceived symptom reduction overtime is underway.
CANNABIS ROLE ON COLORECTAL CANCER: 
A SYSTEMATIC REVIEW OF THE LITERATURE

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Background: Colorectal cancer (CRC) is the third most common cancer worldwide. Several experimental models of diverse types of cancer have demonstrated that cannabinoids may have both antiproliferative and antimetastatic effects. Thus, the objective of this research was to analyze the possible effects of cannabinoids on CRC cells, and their potential to become new therapeutic agents.

Methods: We performed a systematic review using the Prisma checklist to determine the different effects of cannabinoids in CRC tissue. The following databases were consulted: PubMed, Scopus, Embase, and Biblioteca virtual en Salud (BVS). We use the following Medical Subject Headings (MESH) terms: colorectal cancer, colon cancer, Colonic Neoplasms, Colorectal Neoplasms, Hereditary Nonpolyposis, Colorectal Neoplasms, combined with Cannabis, Medical Marijuana, Marijuana Smoking, Cannabidiol, cannabinoid. Eligibility criteria were experimental studies and reviews, publication date between January 1997 and January 2019. A total of 758 articles were identified through databases searching using the MESH. Based on these criteria, 68 articles were chosen.

Results: Diverse cultured colonic cancer cells have an increased expression of cannabinoid receptors such as CB₁, CB₂, TRPM8, and GPR55, and endocannabinoids anandamide (AEA) and 2-arachidonoylglycerol (2-AG). Five in vivo studies in rodents treated with azoxymethane (AOM), have demonstrated that the primary mechanism of cannabidiol, cannabigerol, O-1602, FAAH, and MAGL inhibitors, is apoptosis. Cannabinoids provoke apoptosis through several mechanisms including the increase of ceramide levels, antagonism of GPR55 and increase of reactive oxygen species production. In vitro studies showed that cannabinoids were also able to inhibit survival and growth pathways like RAS-mitogen-activated protein kinases pathway and the phosphatidylinositol 3-kinase pathway. Moreover, AEA significantly inhibited tumor cell growth and induced cell death in COX-2 expressing cell lines through competitive inhibition. Fiore et al. found that rimonabant, (an inverse agonist of CB₁ receptors) is capable of inhibiting the Wnt/β-catenin pathway in both in vitro and in vivo models of CRC with a reduction of several transcription factors involved in tumorigenesis. Contrarily to these findings, in some studies cannabinoids were shown to have tumorigenic effects, as they triggered cell proliferation.

Conclusions: Induction of apoptosis through several mechanisms is the primary action of cannabinoids on CRC. For this reason, cannabinoids have great potential as novel therapeutic agents for CRC. The effects of these substances may depend on the concentration, the type of cannabinoid, and the cell-line used. It is crucial to conduct more studies to understand the different mechanisms of action of cannabinoids, to shed light on its therapeutic potential and its possible benefits when compared with current antineoplastic agents.
CASE REPORT: MEDICAL CANNABIS FOR PAIN CONTROL IN PALLIATIVE CARE UNIT FROM “ANGEL H. ROFFO” ONCOLOGICAL INSTITUTE, AN OBSERVATIONAL PROTOCOL

Dr. Alvaro Sauri & Dra. Romina Montiel et al.
Palliative Care Unit from Angel H. Roffo Oncological Institute, University of Buenos Aires

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During 2017-18 the palliative care unit of the Angel H. Roffo Oncological Institute has accompanied patients using medical cannabis for pain control and other symptoms. A brief report case is presented in which a patient has reduced opioid dosage for pain control, without anti cancer treatment.

Clinical Case: In June 2017 a 76 year old woman came into our unit for pain control. She has a left breast infiltrating Carcinoma, Stage III a, hormonal receptors negative and HER(-) with 17 years evolution. She was admitted in the Observational Protocol “Cannabis and Health” created by the La Plata National University, toxicology department of the Biochemical Faculty & our institute. She had at admission multiple bone, dermic, liver, supra and infra diaphragmatic adenopathies, and pulmonary metastases. She had received various schedules of treatment, but the illness progressed during 2017. She was on 8/10 pain intensity localized in vertebrae regions between D8 to L4, somatic and neuropathic characterizations, received radiotherapy a year ago and now was medicated with weak opioids without optimal response. Her medication was Codeine 30 mg tid, Paracetamol 500 mg tid, Pregabaline 75 mg tid, Ibuprofen 400 mg tid, Dexametasone 4 mg qd. She decided by her own to be medicated with Cannabis Oil to improve her treatment of pain, anorexia and asthenia, which had worsen. The patient was observed during a year. We detected that her Oral Morphine Equivalent Daily Dose (DEMO) decreased 97% in the first 14 days of Cannabis treatment. Her quality of life improved in spite of illness progression.

Method: The used Cannabis oil samples were extracted with ethanol and, after a clean-up process, the cannabinoid profile was analyzed by HPLC-UV/DAD using analytical standards to identify and quantify (Cerilliant).

Results: A drastic reduction of DEMO was observed after 14 days of initiated treatment using 0,5 ml of sublingual Cannabis (THC= 12,92 mg)(CBD= 4,11mg), discontinuing Pregabalin & Paracetamol, keeping only Ibuprofen 400 mg bid. During that year, due to illness development, DEMO increased up to 6 mg, pregabalin up to 100 mg qd, Ibuprofen 600 mg bid and Cannabis 1 ml qd. (THC= 25,85 mg)(CBD= 8,23 mg) While an increase of Codeine was needed, it was lesser than ¼ of the initial DEMO. The patient kept on receiving sublingual Cannabis until 3 days before death. No adverse effects were reported.

Discussion: During 2017-18 we checked on 33 patients who received Cannabis oils or smoked Cannabis for symptom control. The majority was on concomitant oncological treatment. This woman was not affected by this variable.

Conclusion: Evidence of the co analgesic role of Cannabis in pain control was clearly observed in this case. It was of interest that there was no need to include morphine into the schedule, and the other pharmacological parameters were kept reasonably stable. We observed in the majority of patients who received Cannabis Oil referred subjective betterment of pain. These patients were on anti cancer treatment so they were not evaluable to affirm the determinant role of cannabis in pain control.
MARKET ANALYSIS OF CBD OILS AND CANNABIS FLOWERS SOLD IN EUROPE:
CANNABINOIDS, TERPENES AND HEAVY METALS

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Introduction: Given that in general in Europe there is a lack of regulation for cannabis products, which are partly used for therapeutic purposes, there might be products in the market that are not in accordance with their label regarding cannabinoids content or that contain diverse contaminants such as heavy metals. Cannabis plant is known to efficiently uptake soil contaminants like metals. Some metals are toxic even in low concentration under chronic exposure (i.e. Pb, As and Cd), while others are essential but can also be harmful in high concentrations (i.e. Cu, Zn, Fe or Mn).

Objectives: To assess the cannabinoids and terpenes profile as well as concentration levels of heavy metals in cannabis flower and oil samples that are sold in the European market.

Methodology: This study is embedded in a more comprehensive study which assesses environmental contaminants, like pesticides and mycotoxins besides heavy metals in around 150 samples. Sample collection has been conducted in 2019 and were taken both from legal (high CBD plants collected in Italy, Switzerland and in the case of oils also UK) and illegal market (mainly high THC; Spain). In this study we include data for 23 oils and 30 flowers regarding metals and 37 oils and 72 flowers regarding cannabinoids and terpenes. Cannabinoids, terpenes and metals were measured by HPLC-DAD, GC-FID and ICP-MS respectively.

Results: The 43% of flower samples from Italy are above the established maximum THC content in the country (0.6%), whereas all samples in Switzerland fulfill the state requirement of 1%. In high CBD plants average ratio of 25:1 CBD/THC was found, while an average THC/CBD ratio of 630:1 was observed in high THC plants. Many oil samples (42%) had lower CBD amounts than those stated in the labelling and 24% of Italian samples had 200% higher THC concentration than stated. Regarding terpenes, less variation was found in high CBD plants, which have high amounts of myrcene (21% in average) in comparison to high THC plants (12%). In addition, overall terpene content was lower in high CBD plants (1.30% w/w compared to 1.68% w/w).

With regards to metals, median levels for Hg, Pb, Cu, As, Cd and Cr were 32.9, 104.8, 13593.6, 91.9, 102.6 and 31.8 ng/g in the case of plant samples and 8.5, <0.09, 75.7, 8.5, 0.8 and 7.13 in the case of CBD oils. Concentrations of Pb and Cd were above regulated levels for edible plants in 30% and 50% of samples respectively and 7 and 27% above regulation for respirable samples (in California). For most of the metals assessed in plant samples (Pb, Cu, As, Cd, Cr, Al, Ba, Ni, Sb, V, Sr, Co, Ti, W) levels were statistically higher for legal samples compared to illegal samples. It should be noted that legal samples included in this preliminary study are grown outdoors where soil can be contaminated despite the unawareness of the growers.

Conclusion: Due to historical breeding projects, high THC plants can achieve higher THC/CBD ratios and higher variability in terpene profile diversity compared to CBD plants. Overall, low levels of metals were found in oils whereas in few flower samples some metals are above the regulation for edible plants although there is a lack of regulation for plants with smoking/vaporizing purposes. This underlines the importance of developing a regulation framework.
TRANSLATION AND VALIDATION TO THE SPANISH
OF THE CANNABIS USE DISORDERS IDENTIFICATION TEST – REVISED CUDIT-R

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Background: One of the adverse effects of cannabis is the Syndrome due to dependence on the use of cannabis, given the high prevalence of cannabis use for medicinal and recreational purposes and within the framework of a worldwide trend towards legalization, it is necessary to translate and validate the scale of cannabis addiction risk as it will allow us to identify early those patients who will transfer from recreational to medicinal cannabis and are at risk of developing addictive behaviors.

Methods: We made the study by phases. Phase I: Adaptation of the instrument to Spanish, the instrument was translated by a certified translator from English to Spanish. This second version of the CUDIT-R will be evaluated by 4 medical specialists (3 psychiatrists, a toxicologist), who will define if its content is suitable for use in the Colombian context. Version 3 will be translated into English and forwarded to its original authors who will confirm if the scale maintains its original intention and if they agree with the changes made. Phase II: the participants were recruited by Auto applied online survey using and they will be asked to dilute the translated and adapted CUDIT-R, and the symptoms recorded in the diagnostic criteria used in DSMS 5 and modified from AUDADIS 5. Once the responses have been consolidated, collinearity will be assessed through the Bartlett Test and Kaiser-Meyer-Olkin Test. Phase III: Validity of criteria, was evaluated with a correlation between the translated and adapted version of CUDIT-R and the questions of symptoms recorded in the diagnostic criteria used in DSMS 5 and modified from AUDADIS 5. This correlation was made through the Spearman correlation coefficient. Phase IV: Internal consistency, was evaluated using Cronbach’s Alpha and correlation of domains divided in two with the Spearman-Brown formula, with an Alpha greater than 0.7 the internal consistency of the scale will be considered acceptable.

RESULTS: We attained responses from 792 participants that had used cannabis in the last 6 months and eliminated incomplete questionnaires. The analysis was performed on the answer of 465 participants, 37.6% were female and distribution across regions was fairly homogenous.

KMO (0.809) and Bartlett test of sphericity (p<0.05) proved that the variables were correlated and adequate to perform an exploratory factorial analysis. Results of factor analysis are showed in table 1 (removed due to length - please ask the author).

According to values, and parallel analysis, we define to retain two factors, since these two represent over 98% of the variance. We retained two factor loadings, and consider values over 0.3 to define domains of the test. The factor loadings can be seen on table 2 (removed due to length - please ask the author), as well as their Promax rotation. In the unrotated factor loadings, Factor 1 seems to be related to use and effects of cannabis use, and factor 2 seem to be related to thoughts about cessation of consume, this will explain differences. With the Promax rotation, question 1 and 8 seem to be isolated from the rest of the test, with a Cronbach-Mesbah curve we confirmed that question 1 and 8 affected the unidimensionality of the test. Spearman correlation with diagnosis via DSM-V criteria was 0.6079; this correlation improved to 0.6233 when question 1 and 8 were removed. Cronbach’s alpha for the complete test was 0.7225 and considered as acceptable, this parameter also improved to 0.7587 when question 1 and 8 were removed.

CONCLUSION: We validated the CUDIT-R test to be used in Latin-American population. Internal consistency of test was acceptable as well as criterion validity, both of them improved when question 1 and 8 were removed. Question 1 and 8 refer to frequency of use and thought about cutting down use respectively; the observed differences could be related to the fact that frequency of use isn’t related to amount used and severity of the symptoms. This test can be used to identify cannabis use disorder, considering that question 1 and 8 are not optimal for diagnosis, but could provide useful information for patient treatment.
A SYSTEMATIC REVIEW OF THE EFFECT OF MEDICINAL CANNABIS ON INFLAMMATION IN ANIMAL MODELS.

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Introduction: After a long period of prohibition, Cannabis sativa has recently been legalised for medicinal use in more than 30 countries. Until its legalisation, the capacity in which cannabis could be properly studied was severely restricted. More recently, a sharp increase in medicinal cannabis research has occurred and therefore it is important that its therapeutic potential is more comprehensively understood so that appropriate human trials can be planned and executed. A landmark commentary published in ‘The Lancet’ has evidenced the importance of systematic reviews in preclinical studies. The present review will examine the preclinical evidence for medicinal cannabis as a mediator of inflammation in preclinical models. By enhancing our understanding of the therapeutic potential of this plant, more informed decisions can be made when undertaking human trials.

Methods: Six databases were searched for articles reporting on the effects of cannabis on inflammation using in vivo model methods. There were 4,247 eligible full text articles identified, these were assessed against the inclusion criteria, and risk of bias was assessed.

Results: Of the 29 studies that met the eligibility criteria, mice were the most frequently cited models (19), followed by rat (7), pig (2) and macaques (1). Eighteen studies were related to inflammation affecting various organs of the body, and eleven to inflammation within the brain and spinal cord. The majority of these studies demonstrated positive effects on the use of medicinal cannabis (including a range of cannabinoids such as cannabidiol, Δ9-tetrahydrocannabinol, and cannabigerol quinone) for suppressing pro-inflammatory cytokines (e.g., TNF-α, IL-1β) across a range of in vivo models.

Conclusion: Key recommendations, regarding the testing of medicinal cannabis in animal models, are suggested which may be helpful to inform future research in this emerging sector.
This discussion focuses on perceptions of tetrahydrocannabinol as a homeostatic regulating neuromodulator which may produce antidepressant and stress relieving effects when consumed supplementary in appropriate dosages. Rather than causing inherent damage or toxicity we hypothesize THC causes a temporary functional shift - modulation of available resources where memory and habituation processes are weakened while perceived novelty and sensory details are increased. This concept is examined considering data from the effects of THC on sensory gating and P50 Event Potentials. We view alterations of reduced suppression in P50 gating responses in consumers of THC as effects indicating this shift in attentional resources. Data on subjective effects of Cannabis correlates with these effects. Foods that have been commonly consumed may suddenly have more salient qualities tasting more flavorful than usual. Music may sound more detailed and interesting. Colors may appear more vivid. Additionally CB1 Stimulation appears to be strongly connected with feelings of well being in humans from the CB1 dependent effects of Fluoxetine to the ways in which rimonabant, a CB1 antagonist is strongly associated with suicidal ideation. Research shows THC produces antidepressant and anxiolytic effects. Both of these features consistently present when dosage is appropriate. When dosage is too high opposite effects present: feelings of unease, anxiety or paranoia may increase. It is possible anxious thoughts associated with high dose THC may be connected to the memory weakening effects. When these effects are too pronounced familiarity may be reduced in ways where basic assumptions and feelings of comfort are diminished as unknowns increase. THC is a reasonably safe compound for administering antidepressant or anxiolytic effects while lacking the known toxicity of other pharmaceutically available antidepressant and anxiolytic compounds. THC exhibits the ability to be used therapeutically in the treatment of Alzheimer's disease where as traditional pharmaceutical anxiolytics are associated with the ability to enhance possibilities of Alzheimer's and dementia. THC is also not associated with some of the major problematic effects of pharmaceutical antidepressants such as loss of libido. Antidepressant and anxiolytic benefits are goals of homeostasis. It is possible these effects may be connected to letting go of stressors through enhancement of the ability to release or forget them. The increased forgetfulness of THC may be the result of homeostatic resetting of memory circuits. Further more THC’s beneficial homeostasis regulating effects, unless needed for immediate medical administration, may be maximized when THC is consumed through edible ingestion, avoiding inhaled cannabis smoke which presents the potential for disruption of homeostatic balance in the body via the introduction of carcinogens and tars into the respiratory system and blood stream. We hypothesize delayed onset of ingested edible cannabis may also help to circumvent potential for compulsive consumption and allow THC to be more successfully consumed with consistent antidepressant effects while also mitigating tolerance from regular consumption.
ASSESSING THE METABOLIC DIVERSITY OF CANNABIS CHEMOVARS CULTIVATED IN COLOMBIA

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Cannabis is a highly versatile herb with a long history of domestication and use throughout human history. Depending on genetic and environmental factors, cannabis flowers may display a great variety of phytochemicals, many of which have distinct, valuable and often synergistic medical properties. Cannabis plants may be classified in chemovars according to their flower content of phytocannabinoids and terpenoids, secondary metabolites that exert diverse therapeutic effects. Accordingly, patients, physicians, and governmental bodies are giving increased attention to cannabis and, as it exits the shadow of prohibition, a highly profitable medicinal cannabis market trends all over the globe.

However, recent research suggests that non-rigorous breeding practices in the past decades that focused in the production of single metabolites have resulted in the loss of metabolic diversity in modern cannabis chemovars available for patients, narrowing its therapeutic potential.

An innovative legal framework that legitimates the use of cannabis for medicinal purposes, in combination with favorable natural conditions for its cultivation, make Colombia an ideal place for cannabis research. Towards the diversification of medicinal cannabis, we aim to identify phytochemically diverse chemovars that might have adapted to the different environmental conditions throughout Colombia, a world biodiversity-hotspot that has remained unstudied until now. Using a targeted metabolomics approach and state of the art liquid and gas chromatography techniques, we will establish, for the first time, the chemotaxonomic classification of cannabis plants traditionally cultivated in different biogeographical regions of the country.

By harnessing and evaluating the local biodiversity, we intent to set a precedent in a country long stigmatized by a war against illicit drugs towards its transformation into a profitable medicinal chemistry-based industry.
ANALYSIS OF COVARIATES ASSOCIATED WITH SELF-REPORTED CANNABIS USE DISORDER SYMPTOMS

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People suffering from Cannabis Use Disorder (CUD) have generally been studied after diagnosis by physicians. While this is the standard way to identify CUD patients, we wanted to explore potential covariates for a wider population and include people who do not seek professional help. Our aim was to examine covariates for self-reported CUD symptoms.

Data were collected from an online, self-selected survey (www.cannify.us, up to v0.2.5). In the survey, symptoms as described in the DSM-V criteria for CUD were given and the selection of two or more symptoms was used to indicate possible disordered use. Linear regression and logistic regression compared reported negative side effects and CUD symptoms. Logistic regression also compared reported cannabis administration methods and CUD symptoms. Independent two-samples t-tests were used to investigate potential gender differences in the average numbers of negative side effects and CUD symptoms reported.

Linear regression found a strong effect with a weak positive association between the number of negative side effects and CUD symptoms selected (n=1342, β=0.273, p<0.001, R²=0.092). Logistic regression (n=1342) found that those who reported “lack of motivation” were 7% more likely to report ≥2 CUD symptoms than those who did not report that effect (β=0.068, p<0.05). This logistic regression also found associations between people who reported ≥2 CUD symptoms and depression (18.8% more likely to report ≥2 CUD symptoms than those who did not select depression; β=0.172, p<0.01); respiratory illness or discomfort (21.4% more likely; β=0.194, p<0.05); impaired attention, memory, or concentration (7.6% more likely; β=0.073, p<0.05).

An independent two-samples t-test did not find any gender differences in the number of CUD symptoms selected (males: n=910, M=1.213, SD=1.764; females: n=431, M=1.355, SD=1.764, t(1339)=1.42, p>0.05), but did find gender differences in the number of negative side effects selected (males: n=1005, M=1.615, SD=1.933, females: n=508, M=1.972, SD=1.992, t(1511)=3.245, p<0.01, Cohen’s d=0.183).

For administration methods, logistic regression found that those who reported administering cannabis by “dabbing” were 22.9% more likely to have selected ≥2 CUD symptoms than those who did not select that administration method (n=1344, β=0.206, p<0.001).

Based on our data, specific administration methods and the number and type of reported negative cannabis side effects show a relation to potential disordered cannabis use. While we found gender differences in the number of reported negative side effects, we did not find differences in the number of CUD symptoms. This lack of a difference might contrast findings as described in the National Academy of Sciences (NASEM) Cannabis report from 2017 and should be further investigated.
CRITICAL EFFECT OF SOLVENT POLARITY AND DESCARBOXYLATION ON THE BIOLOGICAL ACTIVITY OF CANNABIS SATIVA L. EXTRACTS

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Introduction: Cannabinoids Δ⁹-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the main active compounds in Cannabis sativa L. However, minor non-psychoactive cannabinoids and other non-cannabinoid molecules have been proposed to improve the pharmacological profile of Cannabis extracts compared to isolated THC and CBD. Cannabinoids appear in the plant as their acidic precursors, which readily decarboxylate to neutral forms upon heating. Phytoplant Research S.L. has developed highly productive Cannabis cultivars with defined chemotypes as well as proprietary methods for the extraction and purification of cannabinoids.

Methods: The goal of the present study is to investigate the effect of solvent polarity and the decarboxylation process on the composition and pharmacological activity of Cannabis extracts. To do so, a library of forty Cannabis extracts was generated from ten different cannabis cultivars registered by Phytoplant Research S.L. at the Community Plant Variety Office (CPVO). Plant material was extracted using two different solvents (ethanol and hexane) and subsequently decarboxylated (150°C, 60 minutes) or not. The resulting extracts were analyzed by LC-DAD, with relative amounts of 10 cannabinoids being reported. Biological activity at three molecular targets involved in hypoxia and inflammation (NF-κB, HIF-1α and STAT3) was screened in vitro.

Results: Changes in the transcriptional activation of NF-κB and HIF-1α were found to be variety-specific and solvent-dependent. Further, changes seemed not to be related to cannabinoid abundance but, rather, to the presence of non-cannabinoid molecules selectively extracted depending upon solvent polarity.

Conclusions: Our results indicate that solvent selection and proper decarboxylation represent key aspects for the standardized production of Cannabis extracts with reproducible pharmacological potency.
EFFECTS OF CANNABIDIOL ON THE HEAD-TWICH RESPONSE INDUCED BY 2,5-DIMETHOXY-4-IODOAMPHETAMINE IN MICE

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In rodents, the head-twitch response (HTR) is widely used as a behavioral readout to test the hallucinogen-like effects of compounds, and to measure the effectiveness of antipsychotic drugs in reducing the positive symptoms of schizophrenia such as hallucinations, among others. HTR behavior is specifically linked to 5-HT₂A receptors activation since i) selective 5-HT₂A antagonists block the HTR induced by hallucinogens such as 2,5-dimethoxy-4-iodoamphetamine (DOI) and ii) hallucinogens do not induce HTR in 5-HT₂A knockout mice. On the other hand, cannabidiol (CBD) was found to be effective for the treatment of psychotic symptoms in humans, and was safe and well tolerated, even at higher doses (1500 mg via oral ingestion). However, the molecular mechanisms that mediate this antipsychotic effect remain unknown. To address this question, in this study we characterized the pharmacological effects of CBD in the HTR induced by DOI in mice. Using a pharmacologic approach, we studied the implication of the serotonergic and endocannabinoid systems in the CBD effects on DOI-induced HTR.

Methods: In a 15 min test, a robust HTR was induced in male CD1 mice by subcutaneous injection of DOI (1 mg/kg). To investigate the effect of CBD, five different doses (1, 3, 10, 30 and 100 mg/kg, ip) were given 30 minutes prior to DOI administration. To further investigate the involvement of 5-HT₁A and CB2 receptors on the effects of CBD (10 mg/g) over DOI-induced HTR, a second group of animals were pretreated with selective antagonists WAY-100,635 (0.1 mg/kg, ip) and AM630 (1 mg/kg, ip), respectively, 15 min before the CBD (10 mg/kg) administration.

Results: Our results indicate that CBD significantly (p<0.05) reduce HTR at the all doses tested. This effect was blocked by the co-administration of the 5-HT₁A receptor antagonist, WAY-100,635. Interestingly, the CBD effect was mimicked by the administration of AM630, which caused a similar reduction when given alone, and was able to inhibit the effect of the WAY-100,635, but did not modify the effect of CBD when administered together.

Conclusions: Our results seem to indicate that the DOI-induced HTR in mice is a suitable model to investigate the neurobiological mechanisms underlying the antipsychotic effects of CBD. By using this model, we could demonstrate the implication of 5HT₁A receptors as the responsible of the antipsychotic potential of CBD and to identify CB₂ receptors as modulators of the DOI-induced HTR.
MYCOLOGICAL ANALYSIS OF *CANNABIS SATIVA* L. SAMPLES FOR MEDICINAL USE, IS GAMMA RADIATION NECESSARY?

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**Introduction:** In Italy *Cannabis sativa* inflorescences are commonly used as pharmaceutical ingredients for formulation of galenic preparations in form of extractions or directly weighted in portion of flos for treatment or mitigation of different human health disorders under a medical prescription. All these ingredients, involved in process of formulation by the pharmacist are usually subjected to gamma radiation to lower their microbial contamination, because they have to comply with the limits of microbial concentration reported by pharmacopoeia.

**Aim:** Aim of this research was to identify the best growing and drying condition to obtain inflorescences of *Cannabis* with a low fungal contamination, in order to avoid the gamma radiation step of the preparations.

**Methods:** Inflorescences of *Cannabis* plants were examined after the cultivation in indoor and outdoor conditions dried in three different locations: 1) closed and ventilated room; 2) closed room without any ventilation, 3) a porch; 4) a barn dedicated to straw storage. All dried inflorescences were plated on rich medium in Petri dishes and, after incubation, the colony forming units (CFU) of fungi were counted and identified. As control samples were analyzed three commercial gamma radiated inflorescences used to therapeutic purpose.

**Results:** Results obtained showed that counted CFU for inflorescences outdoor grown were more abundant than ones found in inflorescences indoor cultivated, independently from drying conditions. Among samples grown indoor, those dried in the barn scored higher CFU counting, but the contamination was always lower than limit reported by European Pharmacopoeia. On the other hand, samples outdoor cultivated presented differences in CFU amount according to the different drying method, and the number ranged from \(10^2\) (inflorescence drying in the porch) to \(10^5\) (unventilated closed room). Results showed that the presence of aeration (artificial ventilation in one of the rooms or natural ventilation in the porch) was important for an efficient drying and resulted also in a lower number of CFU when compared to the samples dried in the closed room and in the barn. Gamma radiated samples showed a range of CFU from \(10^2\) (product 1) to \(10^3\) (product 2 and 3), these results suggest that gamma-radiation doesn’t break down necessarily all the fungal flora associated with the inflorescence of medicinal Cannabis.

The isolated fungi belonged to three different genera: *Aspergillus*, *Cladosporium* and *Penicillium*. In samples drying in the ventilated closed room, only *Penicillium griseoroseum* was found, while in the ones drying in the unventilated room there were *P. griseoroseum*, *P. fannelliae* (indoor grown samples) and *Aspergillus ochraceus* (outdoor grown samples). In samples drying in the porch or in the barn, *Cladosporium cladosporioides* and *A. ochraceus* were isolated. *A. ochraceus* was also found in the inflorescences grown outdoor and dried in the unventilated room. It is important to pay attention to the presence of *A. ochraceus* because of its ability to produce ochratoxin A. This mycotoxin is nephrotoxic, carcinogenic, teratogenic, and immunotoxic and it can contaminate cereal and agricultural products. In gamma-radiated inflorescence only strains of *Cladosporium cladosporioides* were isolated from product 1 and 3 while *C. sphaerospermum* were isolated from product 2.

**Conclusions:** In conclusion, all of samples grown indoor present a CFU number that is lower than the limit concentration reported by European Pharmacopoeia for non gamma-radiated samples and in two cases (plants grown indoor and dried in the ventilated closed room or in the porch) lower than gamma-radiated products. These results suggest that close and specific attention to culture and drying method could be an effective possible alternative to radiation of inflorescences.
MEDICAL CANNABIS IN THE TREATMENT OF SPASTICITY ASSOCIATED WITH UPPER MOTOR NEURON INJURIES. LITERATURE REVIEW

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Introduction: Spasticity defined by its two main clinical manifestations that are muscle stiffness and spasms is one of the main clinical problems associated with upper motor neuron injuries, causing a great impact on the quality of life and being one of the main determinants of physical disability in populations affected by this type of injury. Its treatment represents a clinical challenge that begins from its early detection, staging and final treatment, with unsatisfactory results so far, despite the various pharmacological and non-pharmacological approaches used.

Methodology: A literature review was carried out using as search terms “cannabis” “medical marijuana” “cannabinoids” “muscle spasticity” “therapeutics” using pubmed and embase databases, scielo, as well as in clinical trials.gov and, limiting the search articles written in spanish, english and portuguese, emphasizing original articles and those that specified methods of evaluation of spasticity, as well as ongoing studies, without establishing time limit of publications. Results: The initial search yielded a total of 107 articles between January 1980 and January 2019, with a first specific reference of the use of inhaled cannabis in 1997 (Consroe, Paul; Musty, Rik; Rein, Judith; Tillery, Whitney; Pertwee, 1997) and which have been followed by multiple case reports, systematic reviews and 4 randomized studies trying to assess its effectiveness, with a weight of evidence.

Conclusions: Treatment with medicinal cannabis as an adjunctive therapy has shown an irregular efficacy in the control of the signs and symptoms associated with spasticity in patients with upper motor neuron injury, with a lack of standardization of the methods of evaluation and qualification of spasticity and with wide margins of response that vary from high improvement to no improvement and presence of adverse events for patients. However, there is a tendency to improve the quality of life in those subjects who use it. It is necessary to expand the studies with this type of substances better objectifying the way of evaluation of motor symptoms in patients with secondary spasticity lesions of upper motor neuron, as well as possible drug interactions to give greater evidence to the use of a therapy that could show benefits about specific populations with this symptomatology.
USE OF CANNABINOID THERAPY IN PATIENTS WITH REFRACTORY CHRONIC PAIN – A RETROSPECTIVE REGISTRY STUDY OF PATIENTS FOLLOWED IN A DANISH PAIN MANAGEMENT CLINIC

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Introduction: Complex chronic pain disorders cause impairment of daily functionality and reduction of quality of life in most patients. In some patients, adequate symptom relief is not achieved with conventional pain regimens or side effects are intolerable. In this context, cannabinoids are considered as a potential supplementary therapeutic option. This study aims to explore efficacy and tolerability of cannabinoids among patients with refractory chronic pain, and also to assess reduction of conventional drugs following initiation of cannabinoid therapy.

Method: A retrospective registry study has been initiated in a population of almost 2900 patients with refractory pain, prescribed cannabinoid therapy in a Danish pain management clinic from March 2016 until December 2018. In this period patients were prescribed different cannabinoids and/or medicinal cannabis products as whole dried flower, capsule or oil. Data from patient medical records, including referral diagnosis, conventional drug regimen, pain complaints, quality of life and sleep plus level of functionality before and after initiation of cannabinoid therapy, are assessed for further statistical analysis.

Results: An interim analysis of 477 patients has been conducted. These patients were initially prescribed cannabinoids manufactured at Glostrup Pharmacy in Denmark either as tetrahydrocannabinol (THC), cannabidiol (CBD) or a combination of both. Preliminary results showed that more females (74%) than male (26%) were prescribed cannabinoids. Six major diagnostic groups were identified as follows: cancer, multiple sclerosis, neuropathy, fibromyalgia, musculoskeletal pain and other. The prescribed cannabinoid regimens were different in accordance to diagnosis. Patients with cancer or neuropathy were predominantly prescribed THC (56% and 82%, respectively) while patients with fibromyalgia were prescribed CBD (66%). More than 40% of patients continued cannabinoid treatment beyond six months duration. Almost 20% of patients discontinued treatment due to lack of adequate effect. Adverse reactions (9%), costs (7%) and death (7%) were among other reasons to discontinue cannabinoid therapy. Final study results will be ready for dissemination by second half of 2020.

Conclusion: It is expected that this study will add new information on efficacy and tolerability among patients receiving cannabinoid therapy against refractory pain manifestations. Furthermore, this study will apply guidance when prescribing cannabinoids for chronic pain conditions.
PATERNAL ACTIVATION OF CB₂ RECEPTOR IMPAIRS OFFSPRING GROWTH

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In the testis, cannabinoid receptor type 2 (CB₂) is mainly expressed in spermatogonia and its in vitro activation, through the selective agonist JWH-133, promotes meiotic entry and progression. Moreover CB₂ in vivo activation/inhibition in males alters the correct progression of spermatogenesis inducing its acceleration or slowdown respectively. Thus CB₂ receptor signaling in germ cell plays a physiological role in the regulation of spermatogenesis. However, up to now, no information is available on the effects of male exposure to JWH-133 on sperm number, quality and function. In this study we focused on male reproductive success in terms of fertility and healthy pregnancy outcomes.

Methods: CD-1 male mice at 7 dpp were randomly divided into two groups: one group was intraperitoneally injected with JWH-133 (1.5 mg·kg⁻¹) for 5 consecutive days at 24h intervals for five consecutive weeks, the other group treated with vehicle. At the end, mice were sacrificed and sperm number, morphology and motility were evaluated under microscopic analysis. Fertility was investigated by crossing treated or control males with untreated females. Derived embryos and placentas were recovered at E13.5 and E18.5 and morphologically analyzed on histological sections by staining with H&E and PAS respectively. For each group, number, weight and size of pups were tested.

Results: In this study we demonstrate that chronic exposure of male mice to JWH-133 drug is associated with a reduction of testis weight and sperm number without alterations of sperm motility. However variation in sperm count of treated mice was not associated with changes in fertility. Indeed we didn’t observe significant reduction in mating rate, fertility rate and litter size, after crossing of JWH-133 male mice with unexposed females respect with control fathers. Nevertheless we found that offspring from JWH-133 exposed father showed lower weight and size respect with offspring sired from control mice. These growth defects were already evident in E13.5 and E18.5 embryos sired from JWH-133 male mice and maintained postnatally until one month. Moreover these embryo defects correlated with a reduction in size and weight of placentas and were associated with a thinner spongiotrophoblast layer.

Conclusions: In this study we show that paternal activation of CB₂ causes: 1) reduction of sperm count that does not impair fertility 2) offspring growth defects at embryonic and postnatal age. We speculate that growth defects observed both in placenta and embryo from JWH-133 treated male mice could be associated to epigenetic modifications occurred in sperm epigenome and transmitted to the next generation. Further analyses will be necessary to better investigate this correlation. Our results suggest that these alterations transmitted in the progeny by sperm, highlight the potential consequences associated with male exposure to cannabinoid.

CHEMICAL COMPOUNDS OF CANNABIS SATIVA L HAVE DIFFERENT CYTOTOXIC EFFECTS IN HUMAN LEUKEMIC CELL LINES

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Cannabis sativa L contains different metabolites, known as phytocannabinoids that include delta-9-tetrahydrocannabinol (∆-9-THC), cannabidiol (CBD) and cannabigerol (CNG). These molecules have potential therapeutic applications in the management of different diseases such as Alzheimer’s, refractory epilepsy, and multiple sclerosis, as well as, in the control of sideeffects of cancer chemotherapy (Caffarel MM, 2012. Cancer Treatment Reviews, 38 (7). 911-918). Cancer research has also evidenced the potential cytotoxic role of phytocannabinoids, e.g., the ∆-9-THC, in tumor cells by its direct interaction with the endocannabinoid receptor 1 (CB1) (Paweł Śledziński, 2018. Cancer Med; 7(3):765-775.). Moreover, other plant metabolites such as sterpenes and flavonoids enhance their antitumor activity synergistically (Russo, 2011 Br J Pharmacol; 163(7): 1344–1364.). In this work, we evaluated the synergistic cytotoxic effect of cannabinoid- and terpene-enriched extracts in human leukemia cell lines.

Methods: Flowers from ten (M1 to M10) different chemotypes of Cannabis (I, II, III) were collected. Low and median polarity metabolites were isolated by supercritical CO2 extraction. The chemical composition of the extracts was analyzed by gas chromatography-massspectrometry (GC-MS). The cytotoxic activity of the extracts was evaluated in the humanleukemic cell lines U937 and K562; to this purpose, 5000 cells/well in 96-well plates were exposed to a range of concentrations of the Cannabis extracts (200 to 1.6 µg dry wt/mL) for 48 and 72 h. Cell viability was assessed with the MTT [3-(4,5-Dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide] colorimetric assay, and the IC50 (Inhibitory concentration 50%) was calculated for each extract. Results were analyzed with a two-way ANOVA test with a Bonferroni post-test using the GraphPad Prisma 6.0 software.

Results: The extracts with the highest cytotoxic activity (IC50) for the U937 cell line were M3(25 µg/mL), M5 (17 µg/mL), M7 (20 µg/mL) and M8 (30 µg/mL). In contrast, just M7 (25 µg/mL) and M8 (30 µg/mL) were cytotoxic for the K562 cell line. The chemical analysis showed that THC (chemotype I) was the most prevalent metabolite in the M5, M7, and M8 extracts. Besides, the extracts had a high proportion (24%, 35%, and 27%, respectively) of terpenes, being the most abundant, caryophyllene, humulene, and selinene.

Conclusions: The different phytocannabinoid- and terpene-enriched extracts, obtained from Cannabis sativa L, exhibit a differential cytotoxic effect on the leukemic cell lines U937 and K562 after 48 and 72 hours of treatment. Despite its sensitivity to the M7 and M8 chemotypes, the K562 cell line was more resistant to the Cannabis extracts than the U937 cell line. This study shows the synergistic cytotoxic effect of phytocannabinoid (∆-9-THC) and terpenes(caryophyllene, humulene, and selinene) in the human leukemic cell lines, U937 and K562.

More studies are required to describe the nature of the cytotoxic effect (Immunogenic or Tolerogenic cell death) of Cannabis-derived compounds in human leukemic cells.
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