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New designs for cannabis clinical trials (including pragmatic trials and n=1)

Physical and Cognitive Performance Impairment of Cannabis Consumption in Adults Over Time

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Background: The legalization of cannabis in various jurisdictions has heightened the necessity to understand its effects on human capabilities, particularly concerning cognitive and physical performance in the context of safety-sensitive jobs.

Objectives: This investigation aims to elucidate the extent and persistence of impairment caused by cannabis consumption in adults, with a focus on its implications for work performance and safety.

Methods: A group of 14 adults aged between 19 to 44 years, identified as regular cannabis users, underwent a sequence of standardized tests to evaluate cognitive and physical performance. These assessments were conducted before and after the consumption of a cannabis cigarette, with subsequent tests at 1, 6, and 12 hours post-consumption. Blood and urine samples were analyzed for THC and Carboxy-THC concentrations to correlate substance levels with observed impairments.

Results: The study found pronounced elevations in blood THC levels at 1 hour post-consumption, which significantly declined by the 6-hour mark (p 0.001). Changes in Carboxy-THC levels in blood were notable yet less marked ($p = 0.005$), while urine Carboxy-THC levels displayed a non-significant variation over time ($p = 0.068$). Noteworthy were the cannabis-induced increases in systolic blood pressure and heart rate, alongside decrements in motor control, force variability, and overall physical endurance, persisting for up to 12 hours after cannabis intake.

Conclusion: The consumption of cannabis leads to substantial and measurable impairments in both cognitive and physical capacities, which may last for up to 12 hours post-consumption. The study underscores the importance of considering the prolonged effects of cannabis in the formulation of workplace policies, especially for roles requiring high precision and cognitive clarity. Future research should aim to refine impairment assessments, taking into account the individual variability in response to cannabis.

P-02

Assessing safety and adverse events of cannabinoid medications

Smoking a single cannabis joint can impair physiological responses for up to 12 hours with frequent cannabis users

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Background: There are concerns regarding the extent and duration of cannabis effects on work performance and safety.

Objectives: Investigate the extent and duration (12 hours post-consumption) of performance impairments in adult, frequent cannabis users.

Methods: Testing prior to the intervention (smoking a cannabis joint of 3.5-g of dried cannabis, with 15.9-mg/g concentration of Delta-9-tetrahydrocannabinol, and 0.9-mg/g of cannabidiol) and at 1-, 6- and 12-hours after smoking involved measures of perceived feelings of intoxication, blood pressure (BP), heart rate (HR), reaction time (RT), Stork balance test on a padded mat with eyes open, and on a concrete floor with eyes closed, handgrip maximal voluntary isometric contraction (MVIC) force and rate of force development (RFD), maintenance of 10%, 20% and 40% of MVIC for 10-seconds and handgrip endurance test to task failure at 40% MVIC.

Results: Smoking cannabis significantly increased systolic BP (1-hour, p=0.026), HR (1- and 6-hours, p=0.001), force variability when maintaining 40% MVIC (1- and 6-hours, p=0.007) as well as decreases in RFD (50-, 100-, 150- and 200-ms) at all force-time periods (6- and 12-hours, p0.0001), 40% MVIC endurance time (12-hours, p=0.015) and associated endurance task EMG (12-hours, p=0.011) and balance (1-, 6- and 12-hours, p=0.003).

Conclusions: It is recommended that individuals who regularly smoke cannabis should not smoke a single cannabis joint for at least 12 hours prior to activities that necessitate steady submaximal forces, muscle endurance, or high RFD with some caution for balance as well. Individual with chronic tachycardia and hypertension should be cautioned against smoking cannabis.

P-03

Clinical cannabinoid therapy across medical specialties; Pain, Gastroenterology, Palliative Care, Psychiatry and Neurology

Clinical Practice Guidelines for Cannabis and Cannabinoid-Based Medicines in the Management of Chronic Pain and Co-Occurring Conditions

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Methods: We conducted a systematic review of studies investigating the use of CBM for the treatment of chronic pain. Articles were dually reviewed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Clinical recommendations were developed based on available evidence from the review. Values and preferences and practical tips have also been provided to support clinical application. The GRADE system was used to rate the strength of recommendations and quality of evidence. A Strong recommendation was given if the benefit clearly outweighed the risk.

Results: From our literature search, 70 articles met inclusion criteria and were utilized in guideline development, including 19 systematic reviews and 51 original research studies. Publications typically demonstrates moderate benefit of CBM in chronic pain management. There is also efficacy evidence to support the use of CBM to manage comorbid conditions including HIV, multiple sclerosis, arthritis, fibromyalgia depression, anxiety and associated symptoms including disordered sleep, nausea, headache, opioid use and appetite suppression in people with chronic pain.

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P-04

Phytocannabinoid study – strains, chemovars, entourage and molecules

Extraction and chemical characterization of bioactive compounds from non-psychoactive Cannabis sativa L. and assessment of their antiproliferative activity against human glioblastoma cell lines

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Background: Glioblastoma multiforme (GBM) is one of the most frequent malignant primary tumours, characterized by resistance to conventional anticancer drugs, making finding new treatments to fight it of crucial scientific relevance [1].

Objective: By taking into account the growing interest in the antiproliferative activity of bioactive compounds from Cannabis sativa L. [2,3], the aim of this work was to obtain and fully characterize three extracts enriched in cannabinoids (CEF), polyphenols (PEF) and terpenes (TEF), starting from a non-psychotropic hemp variety, and to test their activity on U87MG and T98G GBM cell lines.

Methods: The extracts were prepared from hemp inflorescences, following extraction methods specific for each chemical class. CEF and PEF were analysed in detail by untargeted UHPLC-HRMS, and their main components were quantified by HPLC-UV. Regarding TEF, it was assessed by GC-MS and its compounds were quantified by GC-FID. Then, they were tested for their antiproliferative activity on U87MG and T98G GBM human cancer cell lines.

Results: CEF was able to inhibit cell growth in a concentration and time dependent manner in both cell lines. The IC50 values for CEF on U87MG cells were 32.7 ± 2.3 µg/mL and 19.9 ± 2.9 µg/mL after 24 and 48 h of exposure, respectively. Regarding T98G cells, the IC50 values were 30.8 ± 1.9 µg/mL and 24.2 ± 1.7 µg/mL, after 24 and 48 h of exposure, respectively.

Conclusion: Based on the results obtained, CEF and its cannabinoid components can represent a new promising product against GBM to be further investigated with the elucidation of their mechanism/s of action.

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P-05

Phytocannabinoid study – strains, chemovars, entourage and molecules

Effects of Cannabinoids Abuse on Staphylococcus aureus Infection Susceptibility: An In Vitro and Animal Study

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Abstract

Background: The abuse of cannabis has generated serious health concerns worldwide. Studies have shown that cannabis abuse is associated with the oral infection and may increase the risk of respiratory tract infection. The nature and mechanism of immunomodulation induced by cannabis abuse, however, remains obscure, in particular, in aggravating Staphylococcus aureus (S. aureus, MRSA) associated pneumonia infection. Thus, there is a need to explore the effect and underlying mechanisms by which cannabis mediate immunomodulation in relation to susceptibility to respiratory infection in humans.

Objectives: To determine the effects of cannabinoid on increasing Staphylococcus aureus lung infection in vitro and in vivo and investigate the molecular mechanisms by which cannabinoid increase susceptibility to S. aureus colonization in the lungs.

Methods: This experiment explored and verified the effects of cannabinoid abuse on S. aureus lung infection through in vitro cell experiments (A549 and 16HBE) and in vivo mouse pneumonia models (6-8 weeks old male C57BL/6 mice, 7-day intraperitoneal injection, 1× 108 CFU/40 μl PBS intranasally infection).

Results: Cannabinoid (AEA and CP 55, 940) treatment significantly increased S. aureus adhesion and invasion ability in human lung epithelial cell lines in vitro. However, cannabinoid (AEA, 40 mg/kg and CP 55, 940, 5 mg/kg.) intraperitoneal injection did not deteriorate S. aureus infection in the intranasal pneumonia model.

Conclusion: Cannabinoid (AEA and CP 55, 940) high doses usage increased the S. aureus pulmonary infection and invasion ability in human epithelial cells.

P-06

Clinical cannabinoid therapy across medical specialties; Pain, Gastroenterology, Palliative Care, Psychiatry and Neurology

A Case Report on NHS Funded Medicinal Cannabis for Last Resort Treatment of Chronic Pain

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Background: Cannabis Based Medicinal Products (CBMPs) have been legalised in the UK since 2018. However, only a handful of NHS prescriptions have been written, the majority remain in the private sector. Reasons for this include; restrictive NICE guidance, clinicians` unfamiliarity, lack of robust RCT's and unsubstantiated safety concerns.

Objective: To demonstrate potential benefits of CBMPs when conventional treatments have failed and current challenges accessing CBMPs via the NHS

Methods: The patient identified as a potential candidate for CBMPs had exhausted all conventional NHS treatments. She had also attended all pain management options available including a supported exercise programme. A request was made through the NHS area non-formulary committee for CBMPs as a last resort treatment.

Results: The non formulary committee supported the application provided outcome measures were collected and demonstrated benefit to support an ongoing prescription.

The patient has now been prescribed CBMPs for nine months and reports "life changing" benefit which is reflected in standard outcome measures (Brief Pain Inventory and MYMOP) at 3 and 6 months.

Conclusion: Despite the current challenges faced prescribing CBMPs for NHS chronic pain patients we have demonstrated this can be facilitated through existing NHS pathways and have shown the potential benefits for patients that have not responded to conventional treatments.

P-07

Clinical cannabinoid therapy across medical specialties; Pain, Gastroenterology, Palliative Care, Psychiatry and Neurology

Insights into therapeutic areas with purified cannabidiol, what should we expect for future development

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As the prevalence and impact of certain diseases continues to grow, there is a rising demand for novel therapeutics that will enable the expansion of treatment possibilities and positively impact patient health. To this effect cannabinoid molecules, like cannabidiol have increasingly demonstrated significant potential in pharmaceutical research and development and thus a promising avenue for improving patients quality of life. Understanding how the human endocannabinoid system interacts and regulates different physiological processes and systems in the body has provided insight on how cannabinoids can potentially influence and impact targeted therapeutic areas and provide some guidance on which therapeutic areas would be of most relevance and promise.

Consequently, a review was conducted taking into account different clinical trials that have been performed, ongoing and planned with cannabidiol only, as well as publications, indicators and parameters of early emerging science such as pharmacokinetic studies. The appraisal of the therapeutic evidence base for CBD is complex as CBD products can have additional phytochemical present (like tetrahydrocannabinol THC) which can make the identification of the active pharmaceutical ingredient and the specific benefit of the API challenging. The objective is to map out already established therapeutic areas and elucidate and guide the identification of potential and new therapeutic areas with purified CBD products and where alternative delivery formats (e.g., solid formats such as ODTs and chewables that avoid the gastric path) may be best placed . The results of our research will contribute to also inform the pharmaceutical industry on the appropriate formulations for intended therapeutic areas and expand upon the established therapeutic areas of CBD more effectively.

P-08

Phytocannabinoid study – strains, chemovars, entourage and molecules

The protective effects of cannabinoids and psilocybin on high-glucose, high-lipid-induced dedifferentiation and loss of beta-cells

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High lipid, high glucose (HL/HG) diet can lead to inflammation and cause β-cell dysfunction and loss, leading to type II diabetes mellitus (T2DM). The function of the endocannabinoid system (ECS) has been linked to metabolic illnesses including obesity and diabetes and its complications. Cannabis sativa-derived phytocannabinoids can affect how the ECS functions, suggesting a possible target for the treatment of a variety of diseases, including diabetes. Also, serotonin emerges as a pivotal factor influencing the growth and functionality of β-cells. Psilocybin, a natural compound derived from mushrooms of the Psilocybe genus, exerts agonistic effects on the serotonin receptors; we hypothesized that psilocybin can influence β-cell viability, dedifferentiation, and function.

In this work, we analyzed the ability of pre-treatment of INS-1 832/13 rat insulinoma cells with phytocannabinoids or psilocybin to mitigate HL/HG-induced β-cell loss and dedifferentiation. We exposed INS-1 cells to HL/HG (400 μM palmitic acid and 25 mM glucose) treatment to cause β-cell loss and dedifferentiation. We then pre-treated β-cells with various concentrations of phytocannabinoids THC, CBD, THCV, CBC, and CBN as well as psilocybin and then exposed them to HL/HG and analyzed the potential of pre-treatments to protect β-cells.

Our findings indicate that all five phytocannabinoids reduce HG-HL-induced β-cell loss likely through reducing apoptosis and pyroptosis. The protective effects of CBD, THCV, CBC, and CBN were seen in the glucose-stimulated insulin secretion (GSIS) impairment by HG/HL; CBD was most-effective. Psilocybin administration effectively alleviated HG-HL-stimulated β-cell loss, potentially mediated through the modulation of apoptotic biomarkers, which is possibly related to the mitigation of TXNIP and STAT-1 and STAT-3 phosphorylation. Furthermore, psilocybin exhibited the capacity to modulate the expression of key genes associated with β-cell dedifferentiation, including Pou5f1 and Nanog.

This research lays the groundwork for further exploration into the therapeutic potential of tested natural molecules for T2DM intervention.

P-09

Prediction of response to cannabinoid treatment

Development and application of Drug Efficiency Index metric for the analysis of various omics data sets for post-traumatic stress disorder and treatment resistant depression

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Personalized medicine involves the analysis of omics (transcriptomics, methylomics, metagenomics) data for an individual for precise diagnosis and selection of proper intervention (diet, exercise, nutraceuticals, drugs etc.). The right choice of intervention requires the knowledge of omics response to intervention; unfortunately, the omics data in response to various interventions for various conditions, perhaps except cancer, is still lacking. In the past, we have been involved in the development of several big data analysis platforms, including Oncobox, iPanda, cannabis drug efficiency index (CDEI).

To apply the principles of personalized omics-based medicine to this psychiatric problem, we implemented our drug efficiency index (DEI) for the analysis of the efficiency of cannabis extracts to decrease inflammation in various human 3D tissues, including skin, oral and intestine; inflammation was induced either by UV (skin) or TNF/IFN application. Various extracts were applied to inflamed tissues and transcriptomics analysis was performed. In the particular case of the DEI metric, we evaluate the cannabis extract action according to its ability to restore healthy (control) activation levels of molecular pathways, prior to inflammation. We then used our newly developed algorithm for the analysis of post-traumatic stress disorder (PTSD) and treatment-resistant depression (TRD) cohorts of next-generation sequencing (NGS) and microarray hybridization (MH) gene expression profiles, which in total had 791 samples, including 379 cases, and 413 controls. We have analyzed: (1) cases vs control, (2) before vs after treatment, and (3) responders vs non-responders.

CDEI has been effective in choosing the right cannabis extract for treatment of inflammation.

We found that the DEI values that use the signaling pathway impact activation (SPIA) metric were better than those that used the Oncobox pathway activation level approach for the analysis of response to treatment in PTSD and TRD. We were also able to integrate transcriptomics, methylomics and ncRNAomics data.

P-10

Clinical cannabinoid therapy across medical specialties; Pain, Gastroenterology, Palliative Care, Psychiatry and Neurology

Cannabinoids for Colorectal Cancer Treatment: Exploring the Mechanisms of Synergistic Action of Cannabinoids, Cisplatin, and Intermittent Serum Starvation

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Background: The endocannabinoid system (ECS) controls the growth and development of many cells and cell lineages. Dysregulation of the components of the ECS may result in uncontrolled proliferation, adhesion, invasion, inhibition of apoptosis and increased vascularization, leading to the development of various malignancies. Cisplatin and other platinum-derived chemotherapy drugs have been used for treatment of cancer for a long time and are often combined with other medications. Unfortunately, tumours often develop resistance to cisplatin, forcing scientists to look for alternatives or for synergistic combinations with other drugs.

Objectives: We aimed to explore a potential synergistic effect between cisplatin and major cannabinoids and high-THC Cannabis sativa extract for treatment of various colorectal cancer cell lines.

Methods: We used cell viability assays and global gene transcriptome profiling to unravel the potential molecular mechanisms behind the treatments and their interactions in colorectal cancer (CRC) cell line models. To find potential synergistic interaction, we designed multiple different combinations between cisplatin, cannabidiol, and intermittent serum starvation on CRC lines.

Results: We found that combinations between high-THC cannabis extract and cisplatin worked antagonistically on different CRC lines. These antagonistic interaction between cisplatin and high-THC cannabis extract can be related to changes in the transcription of genes responsible for cell death and cancer pathways related to drug resistance. Most importantly, we found that combinations between cannabidiol and intermittent serum starvation, cisplatin and intermittent serum starvation, as well as cisplatin, cannabidiol, and intermittent serum starvation can work in a synergistic fashion on different CRC lines. Furthermore, we analyzed differentially expressed genes and affected pathways in CRC lines to understand further the potential molecular mechanisms behind the treatments and their interactions. We found that synergistic interaction between cannabidiol and intermittent serum starvation can be related to changes in the transcription of genes responsible for cell metabolism and cancer`s stress pathways (Cherkasova, IJMS, 2023).

Conclusions: These are the first ever data showing the existence and mechanisms of synergistic effects of CBD, cisplatin and intermittent serum starvation on colorectal cancer cells. We, for the first time, show that periodic depletion of cancer cells of primary fuel, glucose, could result in a strong synergy in killing cancer cells by chemo- and possibly radiotherapy when combined with cannabinoids.

P-11

Pharamacokinetics and pharmacodynamics of cannabinoids

The Anti-Inflammatory Effects of Cannabis sativa Extracts and Single Cannabinoids: from Mechanisms of Action to Future Therapeutic Applications

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Background: Over the past decades, the prevalence of chronic autoimmune and autoinflammatory diseases and conditions, such as rheumatoid arthritis, Crohn`s disease, multiple sclerosis, and others has been rapidly growing. The need for safe and effective anti-inflammatory agents is growing, and screening natural anti-inflammatory compounds for clinical application has drawn much attention.

Objectives: We set out to evaluate the anti-inflammatory properties of novel high-CBD cannabis extracts and their components and to establish their modes of action.

Methods: We used human THP-1 macrophages and human small intestinal epithelial cells (HSIEC) to investigate the mechanisms of anti-inflammatory effects of several cannabis extracts, as well as CBD, and three minor phytocannabinoids – THCV, CBC, and CBN using in vitro assays.

Results: Using HSIEC, we showed that high-CBD cannabis extracts suppressed the levels of expression of proinflammatory cyclooxygenase 2 (COX2) and increased the expression of the anti-inflammatory suppressor of cytokine signaling 3 (SOCS3) induced by TNFα/IFNγ application. We revealed that these extracts attenuated induction of proinflammatory interleukin-6 through miR-760- and miR-302c-3p-mediated silencing (Wang, Heliyon, 2023). In THP-1 cells, inflammation induced by lipopolysaccharide application was attenuated by single cannabinoids tetrahydrocannabivarin (THCV), cannabichromene (CBC), and cannabinol (CBN). Our data showed that the mitigation of the PANX1/P2X7 axis plays a significant role in the anti-inflammatory effects of THCV and CBC on NLRP3 inflammasome activation in the THP-1 macrophages model. We also observed that CBC and THCV downregulated the IL-6/TYK-2/STAT-3 pathway and CBN may inhibiting the assembly of the NLRP3 inflammasome by reducing PANX1 cleavage (Gojani, Molecules, 2023).

Conclusion: Our results reveal the mechanisms of proinflammatory effects of cannabis extracts, and the role of major and minor cannabinoids. We also propose the mechanistic basis for the potential use of cannabis extracts and cannabinoids in clinical practice.

P-12

Pharamacokinetics and pharmacodynamics of cannabinoids

The Use of the Cannabis-Responsive Biomarker Database and Machine Learning Applications to Facilitate Successful Medical Cannabis Treatment in Children with Autism

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Autism spectrum disorder (ASD) is a set of neurodevelopmental conditions affecting social interaction and communication. The gold standard to evaluate ASD treatment effectiveness relies on subjective evaluation by a pediatrician, neurologist or psychologist. Medical cannabis (MC) treatment already shows promising results to reduce symptoms of ASD, but data on the mechanism of action and cellular targets of cannabinoids remain unknown, as treatment outcomes are evaluated by subjective observations.

We previously reported the discovery of cannabis-responsive™ (C-Res™) biomarkers, metabolites found in saliva of patients with ASD that change in response to MC treatment. This objective technology defines successful treatment as the shift of C-Res™ biomarkers to the physiological levels detected in healthy people. We confirmed successful MC treatment as observed by a physician in children with ASD by showing the shift of C-Res™ biomarkers from pathophysiological levels towards the physiological levels detected in typically developing (TD) children.

C-Res™ biomarkers create a dynamic, high-resolution and rich feature database for successful machine learning (ML) applications. Here we present the first study in which ML models were applied to: 1) distinguish ASD and TD groups; 2) show the phytochemical entourage effect; 3) identify THC-, CBD- and CBG-specific biomarkers; and 4) identify cannabinoid targets in ASD-dysregulated metabolic pathways.

The potential of the ASD C-Res™ biomarker database, ML applications and bioinformatics tools go beyond precision medicine cannabis treatment. We will also present their potential to bridge other omics technologies to clinical phenotypes of ASD.

P-13

Observational / Epidemiological studies: findings, interpretations, plans

How CBN is utilized in Japan, a country with strict cannabis regulations? Purposes, Medical Effects, Adverse Events and Dependence

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Background: Cannabinol (CBN) was discovered in 1896, but its commercial use did not come into full swing until 2020, and its uses, safety, and efficacy have not been evaluated.Japan has strict regulations on cannabis, but CBN products have been legally distributed since late 2020.They may be used for different purposes and uses than in legal areas such as the U.S., but no academic research has been conducted.

Objective: To conduct a quantitative evaluation of CBN product use, efficacy, dependence, and adverse events by self-assessment in Japan.

Method: An online questionnaire was created for CBN users, and a request for responses was disseminated via SNS.

Results: 515 valid responses were obtained. Regarding purpose, 174 (33.8%) were for medical purposes, 136 (26.4%) for recreational purposes, and 199 (38.6%) for both. The most common details of medical purposes were insomnia (N=325), anxiety (N=186), and depression (N=181). Statistically significant subjective symptom improvement was observed before and after CBN use for insomnia, anxiety, and chronic pain. In addition, 82.7% of users reported improved physical quality of life, 84.1% reported improved mental quality of life, and 55.4% reported improved social quality of life. The rate of adverse events experienced was 9.9%, and 5.2% were classified as substance use disorders.
Conclusions: CBN is used in Japan primarily for self mental-health care applications , not as a prescription basis, and contributes to improved quality of life. The experience rate of adverse events was 10%, the severity was mild, and the dependence was considered milder than that of cannabis.

P-14

Observational / Epidemiological studies: findings, interpretations, plans

A National Survey of Marijuana Use Among US Adults According to Obesity Status, 2016-2022

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Background

Little research has investigated on a population level whether the prevalence of marijuana use differs according to obesity status.

Objectives

To report the prevalence of marijuana in adults from 2016 through 2022, in relation to obesity status.

Methods

This study used a probability sample of US adults aged 18 years and older from the 2016 through 2022 Behavioral Risk Factor Surveillance System (BRFSS), a telephone-administered survey.

Results

The study sample consisted of 845,435 participants in the 2016 through 2022 BRFSS surveys, from US states and territories that completed the optional model on marijuana use. For obese individuals, prevalence of current marijuana use is 25% lower than for non-obese individuals on average. Current marijuana users are consistently less likely to be obese across the levels of age, marital status, race/ethnicity, education, income, employment status, tobacco smoking history, marijuana legalization status, and certain medical conditions (asthma, arthritis, and depression). However, the lower prevalence of marijuana use among obese is only seen in men, not women. In 2022, the adjusted odds ratios of current marijuana use for overweight, normal weight, and underweight adults compared with obese individuals are 1.28 (95% CI 1.16–1.41), 1.63 (95% CI 1.47–1.81), and 1.96 (95% CI 1.48–2.58), respectively.

Conclusion

An inverse dose-response relationship exists between BMI weight classifications and marijuana use, after adjusting for other variables. The lower prevalence of current marijuana use among obese individuals is consistent across levels of medical conditions and other variables. The results further support other research indicating that marijuana use lowers BMI.

P-15

Clinical Registries

Controlled inhalation of THC-predominant cannabis flos improved quality of sleep, general mood, and severity of symptoms in UK civilians diagnosed with posttraumatic stress disorder

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BACKGROUND: Approximately 4% of the UK population experiences PTSD. Individuals must exhibit symptoms across four clusters to receive a diagnosis: intrusion, avoidance, altered reactivity and altered mood.

OBJECTIVES: Evidence suggests that cannabinoid agonists such as nabilone and tetrahydrocannabinol (THC) may alleviate PTSD symptoms. We investigated the safety and effectiveness of THC-predominant cannabis flowers for inhalation to manage PTSD symptoms.

METHODS: We analysed data from the UK patient registry, T21. Validated questionnaires were used to collect PROMs for health-related quality of life (HRQoL), mood/anxiety, sleep, and PTSD-specific symptoms. Inclusion criteria were i) a confirmed diagnosis of PTSD, ii) completed PROMs questionnaires at baseline and at the 3-month follow-up, and iii) received a prescription for a chemotype 1 (THC-predominant) cannabis flower.

RESULTS: Fifty-eight patients were included, 34 of which also had PROMs recorded at 6 months. Most were males (65.5%) with an average age of 39.2 years who had previously used cannabis illicitly (95.6%). At 3 months, participants reported significant improvements in overall health, mood, and sleep quality (P0.001) but not in the proxy for HRQoL (P=0.052). Similarly, participants reported substantial benefits in managing intrusion symptoms (P0.001), mood alterations (P0.001), and reactivity alterations (P=0.002), which were sustained or further improved at 6 months. Participants did not report any side effects associated with CBMPs.

CONCLUSIONS: Inhalation of THC is well-tolerated and useful for managing symptoms of PTSD in cannabis-experienced individuals. However, further research is needed to evaluate the long-term safety and outcomes of controlled inhalation of CBMP in patients naïve to cannabis.

P-16

Observational / Epidemiological studies: findings, interpretations, plans

NHS-Reimbursed Cannabis Flowers for Cancer Palliative Care and Management of Chemotherapy-Induced Nausea and Vomiting: The Mike Roberts Case Report

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BACKGROUND: Chemotherapy-induced nausea and vomiting (CINV) is a debilitating side effect of cancer treatment, affecting up to 40% of patients. Cannabinoid agonists such as nabilone and Δ9-tetrahydrocannabinol (THC) have shown efficacy as antiemetics.

OBJECTIVES: Evidence suggests that inhaling THC-predominant cannabis flowers rapidly controls CINV and may alleviate other cancer symptoms such as pain, anxiety, loss of appetite, wasting syndrome, and deterioration of sleep. We report the case of Mike Roberts, the first NHS patient reimbursed for medicinal cannabis flowers to manage CINV.

METHODS: Medical data were obtained from NHS records and individual funding request forms. Patient-reported outcome measures (PROMs) were collected at treatment initiation and at 2- and 4-month follow-ups using validated scales. The revised Edmonton Symptom Assessment Scale (ESASr) was used retrospectively to assess acute treatment outcomes.

RESULTS: The patient was diagnosed with metastatic rectosigmoid adenocarcinoma and multiple lung metastases. He underwent palliative FOLFIRI chemotherapy and emergency Hartmann`s surgery. Progression of lung metastasis led to the initiation of second line FOLFOX chemotherapy and, eventually, lung ablation. Chemotherapy was associated with severe nausea and vomiting. The patient reported limited efficacy and intolerable side effects from antiemetics Metoclopramide, Aprepitant, Ondansetron, Levomepromazine, and Nabilone. The use of medicinal cannabis flowers improved CINV, allowing the patient to complete the chemotherapy treatment, along with better outcomes in pain, anxiety, sleep, appetite, and overall mood and quality of life.

CONCLUSION: Inhalation of CBMPs may offer valuable support in cancer palliative care within national healthcare systems.

P-17

Assessing safety and adverse events of cannabinoid medications

Adverse Drug Reactions Associated with the Prescription of Oral Cannabis-Based Medicinal Products: A Post-Marketing Pharmacovigilance Study

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BACKGROUND: Like the UK, other countries have authorized the prescription of cannabis-based medicinal products (CBMPs) for their therapeutical use as adjuvants in the clinical management of different types of chronic pain. However, no clinical trials or formal analysis have been conducted to provide evidence on the safety of these specialties in post-marketing stages.

OBJECTIVES: The aim of this study is to characterize the safety profile of five oral CBMPs in a convenience cohort of Peruvian patients, where CBMPs are registered as medications of traditional use.

METHODS: An analysis of reports of adverse drug reactions (ADRs) received by the pharmacovigilance system of a pharmaceutical establishment between March and October 2022 was performed.

RESULTS: A total of 1060 patients who received treatment with CBMPs were included in the study and only 135 (12.7%) reported at least one adverse reaction. Women reported significantly more ADRs than men ($\chi 2$=27.4; P0.001) and most of the ADRs (77.8%) occurred in the first 4 weeks of treatment. The distribution of ADRs associated with each product was proportional to the frequency of prescription of the product and no higher incidence was found in CBMPs containing Δ9-tetrahydrocannabinol (THC). The most frequently reported adverse reactions corresponded to nervous system disorders (47.2%) and gastrointestinal disorders (17.9%), the preferred terms were dizziness (17.9%), drowsiness (12.7%) and dry mouth (5.7%). Ninety-three percent were characterized as "mild" and 50.2% as "possible".

CONCLUSIONS: This is the first systematic description of adverse reactions associated to CBMPs in Peruvian patients in a real clinical setting and confirms the safety profile previously reported for these pharmaceutical preparations.

P-18

2-ARACHIDONOYLGLYCEROL AND ACUTE PAIN FOLLOWING TOTAL KNEE ARTROPLASTY

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Introduction: Total knee arthroplasty (TKA) is one of the most cost-effective and consistently successful surgeries performed in orthopedics. TKA provides reliable outcomes for patients suffering from end-stage, tri-compartmental, degenerative osteoarthritis. However post-surgical pain is still an issue we are trying to address. The endocannabinoid 2-arachidonoylglycerol (2-AG) activates cannabinoid receptors to reduce pain while its hydrolysis by the enzyme monoacylglycerol lipase (MAGL) generates arachidonic acid, the direct precursor to proalgesic eicosanoids. To explore 2-AG/eicosanoid crosstalk in patient-derived tissue, samples of perioperative synovial tissue were collected from TKA patients and pain scores were obtained a baseline and post-surgery. These findings will provide novel insights into 2-AG/eicosanoid crosstalk in humans perioperative tissues and determine the contribution of 2-AG hydrolysis toward the biosynthesis of eicosanoids ex vivo.

Methods: Patient pain score collection: Pain was assessed using the numerical rating scale (NRS. 0=no pain; 10=worst possible pain) pre- and post-operatively.

Mass Spectrometry: Samples were mixed with 5.5ml of 2:1 $CHCl_3$, and then centrifuged. The organic layer was removed and dried down under argon before being resuspended with 120 µl of $CHCl_3$.

Tissue Punch Assay: Tissue is excised from the patient, and incubated overnight. Tissue punches are then incubated with inhibitors or vehicles in DMEM+0.1%FBS for 6 hours. After 6 hours punches are weighed, and the conditioned media is collected for later mass spectrometry analysis.

Results/Conclusions:. Interim analysis has shown synovial fluid samples containing levels of 2-AG, suggesting that perioperative 2-AG levels may predispose patients to develop greater post-operative pain.

P-19

Regulatory, licensing, and development program issues and plans

Using a Four Stage Proportionality Test to Investigate Whether the Inclusion of Cannabis Within UK Drug Driving Legislation is Compatible with Human Rights

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Background:
In 2015, the Road Traffic Act 1988 was amended to include a criminal offence for drivers exceeding a per se zero tolerance threshold of 2ug/L THC in whole blood whilst removing the requirement to prove impairment.
Objectives:
Investigate the background scientific rationale, political motivations, judicial outcomes and the emerging global science.
From a human rights perspective, identify potential incompatibilities with convention rights as set out within the HRA 1998.
Methods:
We used a four stage proportionality test to assess whether the new offence is infringing human rights by asking the questions: Does the offence pursue a legitimate aim; is there a rational connection between the offence and the objective of the measure; is the offence no more restrictive than necessary and; is there, overall, a fair balance between the achievement of the objective and the harm done to the right?
Results:
A global cohort of meta-analysis in relation to prevalence data, crash risk odds ratios, impairment assessment, duration of impairment and the duration of THC levels in blood shows the reliance on blood tests to secure a conviction without any evidence of impairment or recent use breaches the drivers right to a private life (Article 8) in conjunction with discrimination (Article 14).
The inclusion of cannabis within S.5A drastically failed within all four proportionality tests.
Conclusions:
The inclusion of cannabis within S.5A of the Act is incompatible with several convention rights.

P-20

Pharamacokinetics and pharmacodynamics of cannabinoids

In Silico and In Vitro Assessment of the Neuro-modulatory Potentials of Cannabichromene

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Background: Cannabinoids have been reported to be responsible for diverse effects in cannabis users. Tropomyosin receptor kinase B (TrkB), a protein factor essential for neurodevelopment could provide a possible understanding of the mechanism of neuromodulation in young animals through cannabinoid interactions.

Objectives: We investigated mechanisms of modulation of neurosignalling by some cannabinoids using molecular docking and biochemical assays to validate the effects of the most notable cannabinoid.

Methods: Seven cannabinoids were docked against the active site of tropomyosin receptor kinase B (TrkB) using computational tools; Chimera and Pyrx. The cannabinoid with the highest binding affinity (cannabichromene (CBC)) was obtained and used for biochemical study. The effects of three weeks of oral administration of 10 mg/kg body weight dose of CBC on some neurodevelopment biomarkers in the hippocampus and striatum of young male and female Wistar rats were investigated relative to control animals.

Results: Cannabichromene had the highest binding affinity of all cannabinoids (-46.06 kcal/mol) and formed hydrogen bonds with some residues within the active site of TrkB. Neurosignalling enzymes (acetylcholinesterase (AChE) and monoamine oxidase (MAO-A) activities, malondialdehyde (MDA) concentration were significantly (p 0.05) increased, while relative expressions of brain-derived neurotrophic factor (BDNF) and dopamine receptor 1 (DR1) genes were significantly (p 0.05) down-regulated in the CBC groups relative to control. Although behavioral cognitive biomarkers revealed impairment in short-term memory, this may likely reverse over time.

Conclusion: Our results indicate that cannabichromene could modulate neurosignalling in young animals via interaction with the TrkB receptor and this should be further investigated to harness its potential in neuropsychiatry.

Keywords: Cannabis, Cannabichromene, Neurosignalling, In silico, Modulation.

P-21

NON-ORAL APPLICATIONS OF CBD: PILOT STUDIES THAT MAKE SENSE AND REGULAR CLINICAL TRIALS

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Background

The aim of this paper is to present an overview of selected clinical trials based on non-oral application of cannabidiol (CBD) or cannabis in general.

Objectives

Topical applications in dermatology and ophthalmology will be discussed. Furthermore, intravaginal and rectal applications in the form of CBD suppositories will be discussed in the context of gynecological, gastroenterological and urological diagnoses.

Methods

The author will be focused not only on his own preclinical research and clinical observations, but also on previously published studies based on literature search using PubMed, Scopus and WoS.

Results

The preclinical observations on which these clinical trials (see Objectives above) were based will be briefly mentioned. Attention will also be paid to critical assessment with respect to the above-described areas of medicine and translational research.

Conclusion

The integration of CBD and cannabis into standard pharmacotherapy appears to be a complementary approach. To achieve therapeutic efficacy of the non-oral applications, could be important to consider their combination with the oral ones.

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Clinical cannabinoid therapy across medical specialties; Pain, Gastroenterology, Palliative Care, Psychiatry and Neurology

Who uses Cannabis for what? An update on single institution prospective survey among patients with advanced cancer under palliative care: 2016-2022*

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Background and objectives: Cannabis products are increasingly used by cancer patients under palliative care. The study was aimed to obtain current characteristic of Cannabis users in the population of single institution in Poland over 7 years.

Methods: Semi-structured questionnaire about the usage of complementary and alternative medicine (including cannabinoids use) was prospectively presented to all consecutive advanced cancer out patients of our institution.

Results: The final analysis included 433 patients (F: 67,0%, median age: 64, range: 22-94 years); 32 of them used cannabinoids (7,4%), mostly (n=31) after cancer diagnosis. What is worth to describe, not any correlations with cannabinoids use were observed with regard to gender, age, educational level, marital status, current professional activity, monthly in-come level, religious practices participation, alcohol use or at least 6 months abroad stay. Patients whose first-step relatives lived abroad for at least 6 months more frequently used Cannabis (p=0,03215) and similar observations were stated with regard to those representing medical staff (p=0,01365) or having a medical practitioner in their close family (p=0,03540). Patients suffering from advanced pancreatic cancer used cannabinoids more frequently than those suffering from other cancers (p=0,00496). The occurrence of most common anticancer treatment related side effects (fatigue, pain, nausea, vomiting, diarrhea, mood disorders, hair loss) did not correlate with Cannabis use.

Conclusions: Cannabis are still rarely use among Polish patients under palliative care for advanced cancer. The study will continue to obtain more data.

*Who uses marihuana for what ? Results of survey on complementary and alternative medicine use among patients with advanced cancer, EAPC-2019 conference poster presentation *

P-23

Phase 2/3/4 study findings and designs (including special populations)

Study Protocol Abstract: Investigating the Use of Cannabis-Based Medicine for Reducing Breathlessness in Patients with Severe Chronic Obstructive Pulmonary Disease

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Background:
Chronic obstructive pulmonary disease (COPD) can lead to debilitating breathlessness where conventional treatments like inhalation drugs or even morphine is insufficient. However, preliminary research suggests potential effects of tetrahydrocannabinol (THC) in the lung tissue and in the area of the brain connected to perception of breathlessness.

Objectives:
Therefore, this randomized, double-blinded, crossover trial in patients with severe COPD, aims to assess whether Dronabinol, a form of THC, reduces severe breathlessness as compared to placebo.

Hypotheses:
1) Subjects will report lower breathlessness intensity during Dronabinol treatment versus placebo treatment, assessed by using a numeric rating scale (NRS)
2) Higher blood cannabinoid concentrations will correlate with lower NRS scores

Methods:
Thirty patients with severe COPD will be recruited from our pulmonary outpatient clinic. Subjects will undergo one-month treatment periods with both Dronabinol and with placebo in random, blinded sequences. Each treatment period includes a two-weeks titration phase followed by a two-weeks full-dose phase and a two-weeks washout between periods. Over the 3-months study duration, subjects will undergo assessments including NRS, breathlessness and further questionnaires, 6-minute walk test (6MWT), spirometry, activity and sleep monitoring, blood tests, and cortisol levels. The trial is registered with EudraCT number: 2022-004238-20.

Results:
Findings will be recorded and analyzed in accordance with the distribution of data.

Conclusion:
This study pioneers an exploration into Dronabinol`s potential as an add-on treatment for severe breathlessness, offering insights into a novel therapeutic approach for patient with severe COPD.

P-24

Pharamacokinetics and pharmacodynamics of cannabinoids

ART12.11, A Novel Cannabidiol:Tetramethylpyrazine Co-Crystal, Demonstrates a Pharmacokinetic Profile Comparable With Epidiolex® In Rats

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Cannabidiol (CBD) is available as an approved medicine Epidiolex®, an oral solution of CBD in ethanol and sesame oil used for controlling seizures in orphan childhood disorders. However, the wider therapeutic utility of CBD is hampered by its physical and pharmacokinetic properties, including high lipophilicity, polymorphism, poor solubility, and poor oral bioavailability. Artelo Biosciences have developed a patented cocrystal of CBD with the co-former tetramethylpyrazine (TMP; also called ligustrazine), designated ART12.11. We have previously reported ART12.11 offers improvements in, physicochemical, pharmacokinetic (PK; in dogs) and pharmacodynamic properties compared to CBD.

In the fasted state, orally administered ART12.11 as an aqueous suspension had a lower Cmax of parent CBD compared to the Epidiolex®-like formulation, but similar 7-COOH-CBD levels, and similar overall exposure (AUC0-t) to either parent or major metabolite. In the fed state, orally administered ART12.11 demonstrated similar plasma levels of parent CBD and 7-COOH-CBD as the Epidiolex®-like formulation, and similar AUC0-t. When comparing the ratio of 7-COOH-CBD metabolite to CBD parent (M:P ratio), in the fasted state, the CBD aqueous solution had a ratio of approximately 1.8 (1.8 x metabolite vs parent), ART12.11 has a ratio of 0.8 and CBD in the Epidiolex®-like formulation has a ratio of 0.4 (with a reference value of 0.2 for CBD delivered intravenously (i.v)). In the fed state, these ratios were 1.8 (CBD aqueous solution), 0.7 (ART12.11) and 0.5 (Epidiolex®-like formulation). Differences in M:P ratios are likely to be driven by differences in CBD absorption (gut versus lympathic system; affected by feeding) and first pass metabolism.

The unique pharmaceutical properties of ART12.11 translates into increased exposures of CBD and a major metabolite 7-COOH-CBD comparable to an Epidolex®-like formulated CBD. ART12.11 was delivered as an un-optimised aqueous suspension formulation and these results support further solid-dosage form development of ART12.11 targeting similar or greater exposures compared to Epidolex® liquid. The data highlight the importance of the formulation and drug substance used in relation to metabolite formation. Ongoing research at Artelo will now focus on developing an optimised clinical formulation of ART12.11for future studies.