Medical Cannabis and Cannabinoids

Med Cannabis Cannabinoids 2018;1:130–134
DOI: 10.1159/000494812

Published online: November 9, 2018

Cannabis – Phytochemical, Pharmacological and Clinical Evidence

Scientific Symposium

University of Vienna, Austria, November 15, 2018

Abstracts

Organized by

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Breeding and Agronomical Techniques to Produce Medicinal Cannabis

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The breeding of medical cannabis is focused on female plant because it is the source of raw material that patients and pharmaceutical companies actually utilizes. The optimized cannabis genotype is related to the method and the place of cultivation. Great difference derives between the varieties devoted to indoor or outdoor cultivation. In indoor condition is rising the interest for vertical farming and LED light use. It requires a very specialized varieties particularly bushy that fit for this new method of cultivation. In the second condition, the latitude where the growing is realized play an important role in plant yield and method of standardization of the drug. Mediterranean regions have great advantage in term of energy consumption in comparison with northern countries like Canada or Denmark where big companies are investing huge amount of money in cannabis market. The CO_2 balance will play an important role to allow the utilization of large grow rooms and activities that require a great utilization of power that means production of CO_2. The variety and the cultivation method is the condition to optimize the production of medical cannabis. The presentation will offer an overview of the different scenarios that could originate in relation to the Authority decisions regarding the type of cannabis products to produce and utilize: flower or extracts, for example and the qualitative parameters to apply combined with the standardization level and the biological activities of the different certified and registered varieties.

Cannabis Beyond the "*Big Two*" (THC and CBD)": The Biological Potential of Minor Cannabinoids and of Non-Cannabinoid Constituents of Cannabis

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Cannabis (*C. sativa* L.) is a prolific producer of structurally unique secondary metabolites belonging to various biogenetic classes. The inventory of secondary metabolites isolated from Cannabis encompasses now well over 600 different compounds [1], but only few of them are accumulated in significant amounts. Historically, pharmacological interest on Cannabis has focused on Δ^9-THC (tetrahydrocannabinol) and CBD (cannabidiol), that is, on the narcotic principle of marijuana and on the major phytocannabinoid from fiber hemp [2]. These, along with cannabigerol (CBG), are also the first natural phytocannabinoid that were structurally elucidated [2]. Surprisingly, insufficient attention has been payed to the native forms of the two major phytocannabinoids (THCA and CBDA and their isoprenyl esters) to their lower homologues (THCV and CBDV, respectively), and to the very large number (almost 150) of "minor" phytocannabinoids that occur in Cannabis. As a result, large areas of the cannabinome remain totally unexplored in terms of bioactivity [3] or even waiting to be explored and still uncharted, as cogently shown by the constant flow of novel phytocannabinoids regularly appearing in the literature [4]. In addition to phytocannabinoids, Cannabis also produces various structurally unique stilbenoids, including denbinobine, a compound typical of orchidaceous plants and in high demand in the biomedical community [5]. The shortage of studies on these "non-THC, non-CBD" constituents is therefore surprising, given also the growing evidence that Cannabis extracts have a biological profile that cannot be uniquely traced to any single major constituent [6].

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"Cannabis Based Products: Analytical and Product Development Approaches"

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Cannabis is one of the oldest medicinal plants known to man. The interest in cannabis based products and cannabinoids for medical purposes has exploded in the last few years. At The University of Mississippi, under contract with the National Institute on Drug Abuse (NIDA), resides the only cannabis production operation in the United States to provide research materials for investigators around the country. These include marijuana plant material, cigarettes, extracts and purified cannabinoids, made available through the NIDA Drug Supply Program (DSP). Analytical Procedures were validated for quantitating the levels of cannabinoids and terpenes in these products.

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Aside from providing standardized materials for research, a major effort is expended on developing cannabis-based products. Derivatives of both THC and CBD have been developed and formulated in different dosage forms, including ophthalmic preparations, oral preparations, transmucosal delivery systems and suppositories. Evidence of bioavailability of these drugs from these formulations will be presented and the promise of effective products for various indications will be elaborated.

Cannabis and the Endocannabinoid System – A Molecular Love Story

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There is an intimate relationship between the phytochemistry of the plant genus *Cannabis* and the mammalian endocannabinoid system (ECS). Ever since the discovery of cannabinoid receptors in the 1990s, the characterization of this fundamental lipid network in health and disease is ongoing, with major discoveries that were also inspired by plant natural products. After an introduction into the evolution of endo- and exocannabinoids [1, 2], the molecular mechanisms responsible for the meaningful pharmacological actions of cannabinoids will be critically outlined. The ECS is a potential interface between environmental stress and metabolic signals that link with nutrition [3, 4]. As will be shown, there are different strategies to pharmacologically modulate the ECS [5, 6]. Cannabinoids and cannabimimetics exhibit diverse molecular relationships with the ECS, at different stages, but phytocannabinoids are the only ones that have culminated in clinical applications to date.

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GPR55: A Cannabinoid Sensitive Receptor that Promotes Inflammation and Cancer of the Gastrointestinal Tract

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Cannabinoid receptors 1 and 2 (CB1 and CB2) are located in the gastrointestinal (GI) tract and are protective against inflammation. The GI tract also contains receptors that are sensitive to endo- and synthetic cannabinoids, however, they share little homology to CB1 and CB2. We explored the role of one such receptor, the G protein coupled receptor 55 (GPR55), in intestinal inflammation and colon cancer and observed that GPR55 acts differently to CB1. In models of experimental colitis, pharmacological inhibition of GPR55 reduces intestinal inflammation through decreased expression of proinflammatory cytokines and enzymes, such as TNF alpha and COX-2. GPR55 antagonists also reduce the infiltration of macrophages and lymphocytes into the area of inflammation. In models of colitis-associated colon cancer, genetic knockout and pharmacological blockade of GPR55 leads to reduced tumor burden indicating that GPR55 acts as a tumor promoter. This is in contrast to CB1 which has a protective role in colitis-associated cancer. The pro-oncogenic effects of GPR55 likely involve immune cells of the tumor microenvironment because GPR55 knockout mice show an increased number of CD8+ and CD4+ T cells in the tumors. Their presence has been associated with a good prognosis in colon cancer patients. Additionally, tumors in GPR55 knockout mice have a decreased population of myeloid derived suppressor cells (MDSCs), which are known to suppress T cell proliferation and function. Receptors of the GI endocannabinoid system can, therefore, function in an opposite manner which should be considered when targeting cannabinoid receptors for the treatment of GI inflammation and cancer.

Medical Use of Cannabis: Potential and Risks

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In Germany, two cannabis-based drugs are currently approved for a single indication each. The cannabis extract nabiximol is approved in spray form for the symptomatic treatment of patients with therapy-resistant spasticity due to multiple sclerosis. The active ingredient nabilone is approved in capsule form for the treatment of nausea and vomiting in cancer patients undergoing chemotherapy. On the other hand, German govermental health authoritis have legalized the medical use of cannabis, cannabis extracts and cannabis-based medicines for a wide array of divergent indications. Against this background Prof. Schäfer will present results of a novel scientific literature analysis (Cannabis: potentials and risks, CaPRis®) led by the Clinic of Psychiatry and Psychotherapy of the Ludwig-Maximilians-University Munich (PD Dr. Eva Hoch) and supported by the German Ministry of Health which investigated the benefits and risks for both the me-

dicinal and recreational use of Cannabis and cannabis-based medicines by analyzing more than 2,000 studies. The best investigated indications for the medical use of cannabis are spasticity and chronic pain. Spasticity is considered a painful symptom with harmful complications in the course of multiple sclerosis disorders; they may also occur as a result of spinal cord injury. In the meta-analysis by Whiting et al. (2015) there were 14 studies on spasticity, 11 in MS (n = 2,138) and 3 in paraplegia (n = 142). All studies had placebo control arms. Overall, the studies provided a moderate advantage for nabiximole in MS-associated spasticity. Furthermore, the review mentions that nabiximol improved sleep quality more than placebo. Based on follow-ups of 3–15 weeks, the assessment of this large-scale analysis provided "moderate evidence" for an effect in multiple sclerosis-associated spasticity. For the outcome "50% reduction of spasticity at a follow-up of 6–14 weeks" and for the parameter "overall impression" the evidence was assessed only as "low grade". In chronic pain patients the use of cannabis-based medicines is the best studied for neuropathic pain. Petzke et al. (2016) documented in a systematic review of 15 randomized controlled trials with 1,619 participants that cannabinoids were marginally superior in their efficacy to placebo; in their compatibility, however, they were inferior. There was no difference in terms of safety. From this, the authors concluded that in selected patients with neuropathic pain cannabinoids may be considered for short- and medium-term therapy with insufficient effect of first- and two-line therapies. In the case of cancer pain, the additional use of cannabis or cannabis-based medicines showed no additional benefit in several larger clinical trials (Johnson et al., 2010 and 2013) and, therefore, should be regarded as an individual therapeutic trial. It is important to emphasize that cannabis and cannabis-based medicines should not be used as an isolated phaarmacotherapy, but in combination with other, e.g. physiotherapeutic and pain psychotherapeutic, procedures.

Cannabidiol, a Broad-Spectrum Therapeutic Cannabinoid: Emphasis on it's Neuroprotective Properties

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Cannabidiol (CBD) is a non-psychotrophic phytocannabinoid with broad-spectrum therapeutic properties that are beneficial for numerous disorders. In the CNS, CBD treatment has been found to serve as an anticonvulsant, antiemetic, anxiolytic, antipsychotic, antioxidant and anti-inflammatory therapy in experimental models of epilepsy, vomiting and nausea, anxiety, schizophrenia, oxidative injury, and neuroinflammation, respectively. However, these well-known broad-spectrum therapeutic properties of CBD contrast with the fact that the cellular and molecular mechanisms underlying these beneficial effects are yet to be completely identified. Some effects have been related to endocannabinoid-mediated mechanisms (e.g. inhibition of endocannabinoid inactivation, allosteric modulation of cannabinoid receptors), whereas others appear to be exerted by endocannabinoid-independent processes (e.g. binding to serotonin receptor types, adenosine uptake inhibition, targeting nuclear receptors of the PPAR family, modulation of some ion channels). Some CBD derivatives (e.g. fluorinated CBD, CBD quinones, abnormal CBD) obtained by chemical synthesis appear to modify (enhancing or reducing) the therapeutic properties of this phytocannabinoid and may be of interest in order to recruit more information on the mechanisms of action of CBD. In this lecture, the main emphasis will be paid on the neuroprotective properties of CBD, which are being presently subjected to an intense preclinical research in numerous acute and chronic neurodegenerative disorders. Such neuroprotective properties appear to be the consequence of CBD activity against inflammation, oxidative stress, protein aggregation and impairment in glutamate homeostasis. Disorders investigated with CBD treatments include Huntington's disease, in which this phytocannabinoid combined with Δ^9-tetrahydrocannabinol has been recently investigated in a clinical trial to determine its potential as a disease-modifying therapy, unfortunately being not effective despite the positive results obtained in the preclinical testing. CBD treatment was strongly active in experimental models of Parkinson's disease, although the issue has not progressed to the clinical scenario yet, and the same happens in ischemia, in particular in neonatal ischemia. CBD has been also investigated in Alzheimer's disease and amyotrophic lateral sclerosis. In conclusion, the pleiotropic properties of CBD, which enable this phytocannabinoid to be active against the numerous insults that damage neurons in neurodegenerative disorders, have situated CBD treatments in a promising position to serve for the development of novel disease-modifying therapies based on this phytocannabinoid alone or combined with other treatments. The information recruited at the preclinical level is important and demands the translation of these data to the clinical scenario.

Supported by MINECO (SAF2015-68580-C2-1-R) and CIBERNED (CB06/05/0089).

Medicinal Cannabis – Hope or Dope?

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Cannabis versus synthetic or cannabis-based pharmaceutical cannabinoids

Over the past 20 years there have been substantial changes to the cannabis policy landscape. In some countries, the call for prescribed medicinal cannabis meanwhile turned into a real 'hype'. So the potential use of medicinal cannabis and its major cannabinoid constituents Δ^9-tetrahydrocannabinol (THC, dronabinol) and cannabidiol (CBD) for pain, palliative symptom management and neuropsychiatric diseases has gained increasing interest.

Cannabis, which names the whole plant as well as parts of it (flowers, buds, leaves or full plant extracts), has to be clearly distinguished from single cannabinoids that are characterized as (semi-) synthetic or plant-derived, but chemically defined, puri-

fied pharmaceutical compounds (e.g. nabilone; dronabinol = THC, CBD), and cannabis-based medications like nabiximols (plant extracts with a defined and standardized THC and CBD content). Medicinal cannabis and the various cannabinoids or cannabis-based pharmaceutical medications are not the same, and these terms must not be used interchangeably or synonymously!

Unfortunately, 'cannabis' dominates the public discussion, mixing up street trading and recreational abuse with medicinal cannabis use or the therapeutic use of prescribed cannabis-based medications provided from the pharmacy. The discussion is further confused by the fact that THC-free cannabis or only CBD-containing edibles, oils, teas and extracts of mostly unclear cannabinoid content are freely sold as 'cannabis' and aggressively advertised as a panacea against various types of sickness.

The therapeutic use of prescribed cannabis-based compounds (pharmaceutical cannabinoids) has nothing to do with the legislation debate of medical or recreational cannabis use! The scientific literature on pain management almost exclusively reports on pharmacological effects of chemically pure cannabinoids, but not of smoked 'cannabis', in cancer and non-cancer patients.

Cannabinoids in chronic pain, palliative and neuropsychiatric management

For many years, plant-derived and synthetic dronabinol (THC, one of the major ingredients of cannabis), and the synthetic THC analogue nabilone are available on prescription in several European countries. Sublingual nabiximols spray (Sativex™) containing a combination of cannabis-based THC and CBD has been registered for spasticity in many European countries, long after its approval for cancer pain, central neuropathic pain or spasticity in Multiple Sclerosis (MS) by the Canadian authorities [1, 2]. Early randomised trials proved dronabinol comparable or even better than conventional antiemetics for chemotherapy-induced nausea and emesis. Nevertheless, cannabinoids are not a first-line option as antiemetics.

To date, the potential role of the pharmaceutical cannabinoids nabilone, dronabinol and nabiximols is controversially discussed in cancer pain management and has to be described based on the slowly growing clinical evidence [1]. In cancer pain management cannabinoids work rather as add-on analgesics with opioids and not as replacement of classical pain treatments according to the WHO ladder. Available evidence is also poor concerning the potential benefit of high-dose CBD in cancer and cancer pain treatment [2].

Several controlled clinical trials have clearly demonstrated that oral dronabinol or its combination with cannabidiol (nabiximols) significantly reduced central or peripheral neuropathic pain. Inconsistently, also movement and functioning were improved. As a consequence, a most recent position paper of the European Pain Federation EFIC considers cannabis-based medicines a third-line therapy for chronic neuropathic pain [1]. In exceptional cases of non-neuropathic benign chronic pain, cannabis-based medicines can be considered as an individual therapeutic trial, if all established treatments have failed and after careful analysis and multidisciplinary assessment [1].

Medicinal cannabis: dope rather than hope!

Contrary to many assertions and massive propaganda in favor of medicinal cannabis, there is insufficient evidence of its superior efficacy, tolerability and safety compared to cannabis-based medicines [1, 2]. If a patient is suited for a trial with cannabis-based medicines, oral or oromucosal preparations (e.g. dronabinol, nabiximols, CBD) are recommended to date [1, 2]. In general, cannabis-based or synthetic cannabinoids are an effective add-on medication in certain chronic pain conditions, e.g. neuropathic pain, but not against acute pain [3]. There is still rather weak evidence on the true utility of cannabinoids in cancer pain patients [1]. Recently, the hope in cannabis-based medication has been strengthened by the fast track FDA approval of cannabis-based CBD (Epidiolex™) for the treatment of rare epileptic syndromes [2]. There is more hope on additional promising CBD indications, such as schizophrenia, GvHD and others to come [2].

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