Expert Opinion

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IACM 2nd Conference on Cannabinoids in Medicine

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The International Association for Cannabis as Medicine 2nd Conference on Cannabinoids in Medicine focused on new clinical research with cannabis and single cannabinoids (Δ^9-tetrahydrocannabinol, CT-3) and on animal research with possible therapeutic implications. The meeting brought together basic researchers, clinicians and physicians to facilitate an exchange of knowledge and experience in this field. Even a talk by a patient with multiple sclerosis was included in a workshop on neurology. Current clinical research with cannabinoids focuses mainly on chronic pain and neurological disorders adding to accepted indications such as anorexia in AIDS-wasting and antiemetic effects in cancer chemotherapy. First results are promising and larger studies are underway or have recently been completed and are awaiting publication. New basic research opens further areas of possible uses for modulators of the endogenous cannabinoid system, including osteoporosis, cancer and inflammation. A workshop on psychiatry focused on effects of cannabis use on onset, incidence and the course of schizophrenia. Basic and clinical research shows that adolescents might be more vulnerable than adults to possible psychiatric effects of cannabinoids. It was concluded that possible side effects of cannabinoids should be taken into account but do not preclude a legitimate medical use.

Keywords: adverse effects, basic research, cannabinoids, cannabis, circulation, endocannabinoids, HIV, neurology, neuroprotection, pain, schizophrenia, THC, therapeutic use

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1. Introduction

Since the detection of an endogenous cannabinoid system with at least two subtypes of cannabinoid receptors and their endogenous ligands, fatty acid derivatives, called endocannabinoids, the interest in cannabinoid research and possible therapeutic implications has considerably increased. Many cannabinoid effects are mediated by cannabinoid-1 (CB1) receptors, including psychical and behavioural effects, analgesia, increase in appetite and muscle relaxation. CB1 receptors are found in high concentrations in the CNS, but also in a number of peripheral organs and tissues. Activation of the cannabinoid-2 (CB2) receptor, causes immunosuppression including anti-inflammation. CB2 receptors are mainly expressed by cells of the immune system, including, leucocytes, the spleen and tonsils [1,2].

Pharmacologically the most relevant compound of the cannabis plant, the (-)-trans-isomer of Δ^9-tetrahydrocannabinol (Δ^9-THC) binds to both CB1 and -2 receptors. In a therapeutic context this natural cannabinoid is usually referred to as dronabinol. Today only dronabinol and the THC derivative, nabilone, are legally available for therapeutic uses in some countries, including the US, Canada and several European countries. Additionally, since September 2003, government-licensed cannabis is available in Dutch pharmacies. Two European groups are conducting clinical research with the intent to get license application of cannabis-based drugs –

the British company, GW Pharmaceuticals for several sublingual sprays and the Berlin-based Institute for Clinical Research for a capsulated cannabis extract. Another important research centre is the Center for Medicinal Cannabis Research at the University of California.

The International Association for Cannabis as Medicine (IACM) was founded in 2000 to facilitate exchange between researchers in this field and disseminate information on the therapeutic potential of cannabis and the cannabinoids. The IACM 2nd Conference on Cannabinoids in Medicine was held at the Cologne Medical School in cooperation with the Department of Psychiatry and Psychotherapy and the Department of Anaesthesiology of the University of Cologne.

2. Reviews

2.1 Neuroprotection

R. Mechoulam (Hebrew University Medical Faculty, Jerusalem, Israel) gave an overview on the neuroprotective effects of cannabinoids [3]. The endocannabinoids anandamide and 2-arachidonylglycerol (2-AG), as well as some plant and synthetic cannabinoids, exhibit neuroprotective effects after brain injury or ischaemia. Cannabinoid-receptor agonists inhibit glutamatergic synaptic transmission and reduce the production of TNF and reactive oxygen intermediates, which are factors responsible for causing neuronal damage. The formation of the endocannabinoids is strongly enhanced after brain injury and there is evidence that these compounds reduce the secondary damage incurred. Some plant and synthetic cannabinoids, which do not bind to the cannabinoid receptors, have also been shown to be neuroprotective, possibly through their direct effect on the excitatory glutamate system and/or as antioxidants. Dexanabinol, a non-psychotropic THC derivative, is under clinical investigation in Phase III studies in head trauma patients in several European and other countries.

2.2 Antitumour effects

V. Di Marzo (Istituto di Chimica Biomolecolare, Pozzuoli, Italy) gave an overview on the possible use of endocannabinoid-based therapeutic drugs against tumour growth [4]. Evidence has been accumulated in the past 5 years suggesting that endocannabinoids and particularly anandamide and 2-AG, can influence the decision of the cells to survive and hence, proliferate, differentiate or die. Following early evidence that Δ^9-THC and other phytocannabinoids, can inhibit the proliferation of cancer cells, it was investigated whether and through what mechanisms, anandamide and 2-AG inhibit tumour growth. Evidence so far shows that endocannabinoids, endocannabinoid analogues, THC or other exogenous cannabinoids inhibit the proliferation of human breast and prostate cancer cells, rat thyroid carcinoma cells, human colorectal carcinoma cells, glioma cells, lymphoma cells and skin tumours. Mechanisms of action include activation of CB1 or CB2 or both receptors, inhibition of angiogenesis, inhibition of the activity of the K-*ras* oncogene product. It has also been shown that the levels of endocannabinoids and of their receptors can change in some tumours and cancer cells compared to the corresponding healthy tissues and cells, suggesting that endocannabinoids might tonically control cancer cell growth.

2.3 Circulation

Within the workshop on circulation J. Wagner (Medical School of the University of Würzburg, Germany) gave a review on the effects of cannabinoids on circulation, including effects of endocannabinoids on blood pressure and vascular tone in circulatory shock and on the development of congestive heart failure post myocardial infarction [5]. Daily application of the synthetic cannabinoid, HU-210, after experimental infarction in rats prevented the drop of left ventricular systolic pressure and endothelial dysfunction. However, the cannabinoid also increased left ventricular end-diastolic pressure, which may have a negative impact in the long term. Conversely, a selective CB1-receptor antagonist reduced contraction ability after cardiac infarction. Taken together with other results their studies show that endocannabinoids exert a protective effect following myocardial infarction.

3. Preclinical research

3.1 Infarction

According to research presented by W. Ford (Cardiff University, Cardiff, UK) anandamide limits myocardial infarction associated with ischaemia reperfusion [6]. In hearts of male rats, 30 min of global, no-flow ischaemia was initiated. Anandamide or its vehicle, was infused for 5 min before and after ischaemia throughout the 2 h of reperfusion. In vehicle-treated hearts, infarct size was 20% of the left ventricle, while anandamide significantly reduced infarct size to an average of 11% of the left ventricle. The protection afforded by anandamide was abolished by co-treatment with a CB1 or -2-receptor antagonist, suggesting that this effect is mediated via interaction with CB1 and CB2 receptors but additional mechanisms may be involved.

3.2 Inflammatory bowel disease

E. Fride (College of Judea and Samaria, Ariel, Israel) investigated possible therapeutic applications of the non-psychotropic phytocannabinoid cannabidiol (CBD) and its analogues in mice [7]. Some of the findings include, none of the (-)CBD analogues had any central effect but all except two inhibited intestinal motility. With one exception (+)CBD derivatives were not centrally active and all (+)CBD derivatives induced a complete arrest of defecation, except (+)CBD itself. (+)CBD analogues completely suppressed the inflammatory phase of formalin-induced pain. Fride concluded that some of the CBD analogues devoid of central effects show therapeutic potential as anti-inflammatory drugs for the gastrointestinal (GI) system, with application in conditions such as inflammatory bowel disease and Crohn's disease.

3.3 Bone formation

The work of R. Mechoulam *et al.* on the role of the cannabinoid system in bone formation started from two striking features among the multitude of clinical characteristics of osteoporosis; gonadal failure causes bone loss and obesity protects from bone loss [8]. The peptide, leptin, is known to negatively regulate both osteoblastic and cannabinoid activity. In initial observations, it has been noted that reverse polymerase chain reaction (RT-PCR) of differentiating osteoblastic precursor cells demonstrates progressive increase in mRNA levels of CB2 but not of CB1. In addition, normal mice systematically treated with 2-AG or with a specific CB2-receptor agonist showed a dose-dependent increase in trabecular bone formation. On the basis of these initial data, it was assumed that endocannabinoids stimulate bone formation.

3.4 Depression

CBD, Δ^9-THC and cannabichromene extracts were investigated in the mouse tail suspension test of depression by R. Musty (University of Vermont, Burlington, USA) and R. Deyo (Winona State University, Winona, USA) [9]. Each mouse was suspended from a bar by the tail using adhesive tape. Antidepressant effects are indicated by an increase in the frequency of struggling (activity) or decrease in activity (immobility) during the test. THC produced significant reductions in the number of movements and significant increases in the amount of time spent immobile. CBD produced behaviours that were consistent with imipramine (i.e., elevated activity). Moderate doses of cannabichromene (CBC) produced behaviours that were consistent with imipramine on the tail suspension test (i.e., elevated activity). It was concluded that CBD and CBC may have therapeutic potential in relieving depression.

4. Clinical research

4.1 Spasticity

U. Hagenbach (Rehab Basel, Centre for SCI and Head Injury, Switzerland) investigated the effects of oral and rectal Δ^9-THC on spasticity in patients with spinal cord injury in two open and one randomised, double-blind, placebo-controlled clinical trial [10]. In the open Phase I trial, 22 patients received dose-adjusted dronabinol (mean: 30 mg) over a course of 6 weeks. In the open Phase II trial, 8 patients received rectal dose-adjusted THC-hemisuccinate (43 mg on average) for 6 weeks. The Phase III trial was a double-blind, clinical trial with 13 patients who had already participated in Phase I. They received oral THC in an individual dose determined in Phase I or placebo. In all phases of the study, a significant reduction of spasticity using the Modified Ashworth Scale was measured. In the placebo-controlled phase spacticity scores, for the dronabinol group were 7.21 points compared to the placebo group (12.10 points) ($p = 0.001$).

W. Notcutt (James Paget Hospital, Great Yarmouth, UK) gave an overview on trials conducted by GW Pharmaceuticals in multiple sclerosis, spinal cord injury, cancer pain, neuropathic pain and rheumatoid arthritis. The main outcome parameters were pain severity and spasticity, further parameter included sleep quality and bladder function. Several Phase II or III trials with encouraging results have been completed and results have been submitted for publication in peer-reviewed journals.

J. Zajicek (Peninsula Medical School, Plymouth, UK) presented the study design of a recently completed double-blind, three-arm, multi-centre study with capsulated cannabis extract, dronabinol and placebo in 657 multiple sclerosis patients with muscle spasticity, sponsored by the British Medical Research Council. Results of this largest ever conducted study with oral cannabis are expected to be published soon [11].

4.2 Pain

D. Abrams (University of California, USA) presented results of an open-label pilot study on smoked cannabis in 16 HIV patients with persistent painful peripheral neuropathy despite an opioid analgesic [12]. Excellent correlation was seen between the response to smoking cannabis in the effect on both the chronic neuropathic and an acute experimental pain model. Overall, 10 of the 16 participants experienced a > 30% reduction in their neuropathic pain after 7 days. This allowed investigators to proceed with a current randomised, placebo-controlled trial with a target sample size of 50 subjects. Additional controlled trials of smoked cannabis for HIV peripheral neuropathy are being conducted by other University of California Center for Medicinal Cannabis Research Investigators.

A. Holdcroft (Imperial College London, UK) investigated the effects of a capsulated cannabis extract in postoperative patients [13]. Results of an open-label study with 57 patients aimed at determining the effects of increasing doses on pain relief and side effects following the administration of a single dose containing either THC 5, 10 or 15 mg were presented. A double-blind, multi-centre, study with 400 postoperative patients receiving a cannabis extract with THC 10 mg is currently underway.

Another dose-finding study was carried out at the Lukas-Clinic in Arlesheim, Switzerland, in 40 palliative cancer patients under the guidance of S. Helwig [14]. The maximally tolerated dose (MTD) of standardized cannabis extract (CE) in this patients group was found to be THC 0.15 mg/kg body weight. A total of 27 patients documented mood elevation on visual analogue scales in their diaries, 24 increase of appetite, 20 relief of pain and nine relief of nausea: no patient reported a worsening of symptoms.

U. Schneider (Medical School of Hanover, Germany) presented results of a double-blind study on CT-3, a non-psychotropic derivative of the THC metabolite, THC-COOH, in 21 patients with chronic neuropathic pain [15]. They were randomised to two 7-day treatment orders in a crossover design and received either CT-3 20 or 40 mg b.i.d. or placebo. Pain scores, as measured by visual analogue scales, improved significantly; transit dry mouth and tiredness were reported signifi-

cantly more often than in the placebo treatment week. No adverse psychological or major physical effects were observed.

4.3 Night vision

Inspired by reports on improvement in night vision among Jamaican and Moroccan fishermen after ingestion of herbal cannabis E. Russo *et al*. (Montana Neurobehavioural Specialists, Missoula, USA) investigated this effect under double-blinded conditions with THC (2.5 – 20 mg) and in field studies in Morocco [16]. A portable device, the LKC Technologies Scotopic Sensitivity Tester-1 (Gathersburg, MD, USA) was used to measure dark adaptometry and scotopic sensitivity. Dose-dependent improvements in night vision measures were noted after THC or cannabis. It is believed that this effect is dose-dependent. Possible clinical application of the results in nyctalopia, retinitis pigmentosa or other clinical conditions were discussed.

5. Side effects

One of the workshops during the meeting focused on psychiatric side effects of recreational cannabis use, which may have implications on its medical use. F.M. Leweke (University of Cologne, Germany) presented research on the role of endocannabinoids in psychiatric disorders [17]. Cerebrospinal concentrations of specific endogenous cannabinoids are significantly higher in schizophrenic patients never treated with neuroleptics than in healthy controls. This may reflect an imbalance in endogenous cannabinoid signalling, which may be either a specific reaction to or a pathophysiological condition in schizophrenia itself. C. Henquet (Maastricht University, The Netherlands) noted that cannabis use by adolescents and young adults may increase the risk for the development of psychosis in later life. M. Schneider and M. Koch (University of Bremen) presented a poster on animal research, which showed that puberty in rats is a vulnerable period for adverse effects of cannabinoid treatment [18]. Peripubertal cannabinoid treatment resulted in a long-lasting deficit in prepulse inhibition, which might serve as an animal model for anhedonia. This deficit was reversed by the acute administration of haloperidol. They propose chronic cannabinoid administration during pubertal development as an animal model for at least some aspects of schizophrenia. D.H. Linszen (Adolescentenkliniek ACM/De Maaren, The Netherlands) presented research demonstrating that cannabis use has a negative impact on the course and outcome of schizophrenia.

Another area of concern is the long-term effect of cannabis use on cognitive function. Whether marijuana produces cognitive dysfunction beyond the acute intoxication period is equivocal in large partly due to methodological and interpretative limitations. A major issue when interpreting the putative impact of marijuana is the role of confounding variables. P. Fried (Carleton University, Ottawa, Canada) is the lead researcher of the Ottawa Prenatal Prospective Study (OPPS) [19]. Participants have been evaluated since birth and are currently an average of 20 years of age. Of the 97 subjects in the present report, ~ 20% are currently using marijuana at least five times per week, 20% regularly but less than five joints per week and the remaining subjects have smoked it fewer than three times and have not used it in the past 3 months. Processing speed and immediate memory were impacted by heavy regular use but not light use. Neither long-term memory nor working-memory was associated with heavy use. The impact of the drug was highly similar in the two sexes in all the cognitive domains considered.

6. Expert opinion and conclusion

Many people who suffer from severe illnesses have discovered cannabis as a beneficial remedy and surveys in Europe and North America show that an increasing numbers of citizens in several countries reject criminal prosecution of patients who benefit from the drug. The psychotropic effects of CB1-receptor agonists and the stigma of cannabis as a recreational and addictive drug are still major obstacles to the legal therapeutic utilisation of the whole range of potentially beneficial effects. However, long-lasting effects on psyche and cognition that might occur with cannabis use are either rare or subtle and do not preclude a legitimate medical use of cannabinoid based drugs.

Aside from phytocannabinoids and cannabis preparations, cannabinoid analogues (that do not bind to the CB1 receptor are attractive compounds for clinical research, namely CT-3 and dexanabinol.) Additional ideas for the separation of the desired therapeutic effects from the psychotropic action comprise the concurrent administration of THC and CBD and the development of compounds that influence endocannabinoid levels by inhibition of membrane transport or hydrolysis.

So far, clinical research showing therapeutic effects of cannabis or THC has been published for anorexia and cachexia, nausea and vomiting, chronic pain, spasticity and muscle spasms, movement disorders such as Tourette's syndrome and L-DOPA-induced dyskinesia, asthma and glaucoma [20]. However, studies were often small and sometimes inconclusive. Properly designed and executed clinical studies are underway to add to the available data and to verify anecdotic experiences and results from smaller uncontrolled studies. Recent results are encouraging.

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101. http://www.cannabis-med.org
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